HETEROCYCLIC PPAR MODULATORS

BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor superfamily, a large and diverse group of proteins that mediate ligand-dependent transcriptional activation and repression. Three subtypes of PPARs have been isolated: PPARα, PPARγ and PPARδ.

The expression profile of each isoform differs significantly from the others, whereby PPARα is expressed primarily, but not exclusively in liver; PPARγ is expressed primarily in adipose tissue; and PPARδ is expressed ubiquitously. Studies of the individual PPAR isoforms and ligands have revealed their regulation of processes involved in insulin resistance and diabetes, as well as lipid disorders, such as hyperlipidemia and dyslipidemia. PPARγ agonists, such as pioglitazone, can be useful in the treatment of non-insulin dependent diabetes mellitus. Such PPARγ agonists are associated with insulin sensitization.

PPARα agonists, such as fenofibrate, can be useful in the treatment of hyperlipidemia. Although clinical evidence is not available to reveal the utility of PPARδ agonists in humans, several preclinical studies suggest that PPARδ agonists can be useful in the treatment of diabetes and lipid disorders.

The prevalence of the conditions that comprise Metabolic Syndrome (obesity, insulin resistance, hyperlipidemia, hypertension and atherosclerosis) continues to increase. New pharmaceutical agents are needed to address the unmet clinical needs of patients.

PPARδ agonists have been suggested as a potential treatment for use in regulating many of the parameters associated with Metabolic Syndrome and Atherosclerosis. For example, in obese, non-diabetic rhesus monkeys, a PPARδ agonist reduced circulating triglycerides and LDL, decreased basal insulin levels and increased HDL (Oliver, W.R. *et al.* Proc Natl Acad Sci 98:5306-5311; 2001). The insulin sensitization observed with the use of a PPARδ agonist is thought to be in part due to decreased myocellular lipids (Dressel, U. et al. Mol Endocrinol 17:2477-2493; 2003).

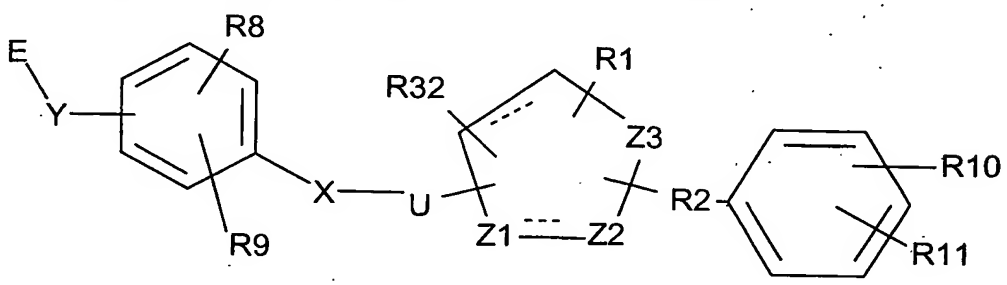
Further, atherosclerosis is considered to be a disease consequence of dyslipidemia and may be associated with inflammatory disease. C-reactive protein (CRP) production is part of the acute-phase response to most forms of inflammation, infection and tissue damage. It is measured diagnostically as a marker of low-grade inflammation. Plasma CRP levels of greater than 3 mg/L have been considered predictive of high risk for coronary artery disease (J. Clin. Invest 111: 1085-1812, 2003).

PPARδ agonists are believed to mediate anti-inflammatory effects. Indeed, treatment of LPS-stimulated macrophages with a PPARδ agonist has been observed to reduce the expression of iNOS, IL12, and IL-6 (Welch, J.S. et al. Proc Natl Acad Sci 100:6712-67172003).

It may be especially desirable when the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile. In some instances, it can be desirable when the active pharmacological agent selectively modulates more than one PPAR receptor subtype to provide a desired pharmacological profile.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18,

R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, NH, and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4

cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are

each optionally substituted with from one to three independently selected from R28;

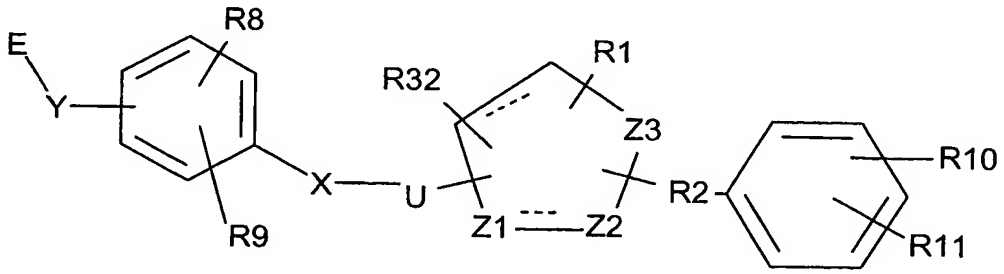
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

A further embodiement of the present invention is a compound of the Formula I'':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-

alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three

independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

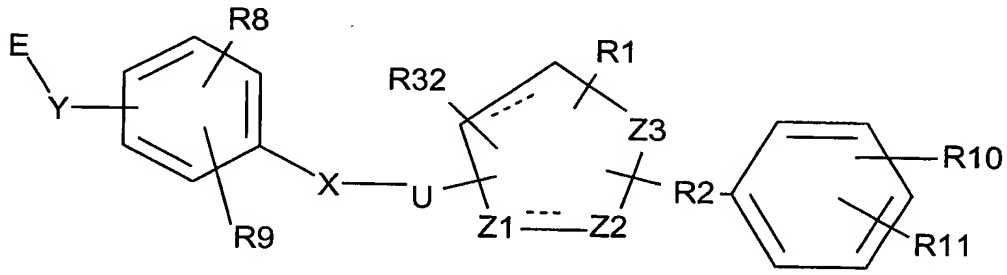
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

Another embodiment of the present invention is a compound of the Formula I''':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13,

COOR14, $OC(O)R15$, $OS(O)_2R16$, $N(R17)_2$, $NR18C(O)R19$, $NR20SO_2R21$, SR22, $S(O)R23$, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of O, S, NH, C, and a single bond;

(g) E is C(R3)(R4)A; wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6

cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

with the proviso that when Y is O then R4 is selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano,

nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2$R16', $N(R17')_2$, NR18'C(O)R19', NR20'SO_2R21', SR22', S(O)R23', $S(O)_2$R24', and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

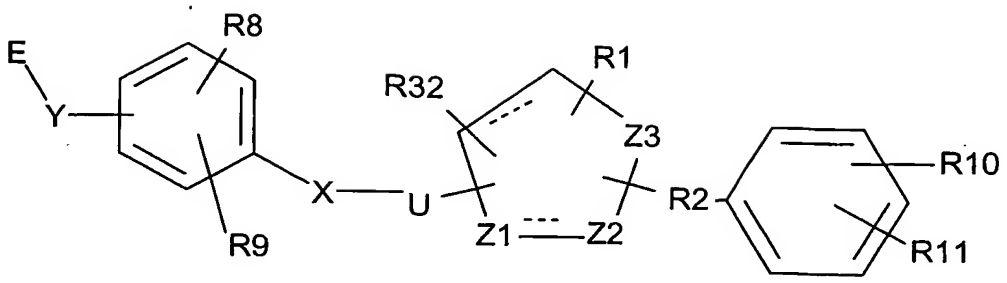
(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

Another embodiment claimed herein is a compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$;

R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each

independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally

substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-

alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

In one embodiment, the present invention also relates to pharmaceutical compositions comprising at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate, or stereioisomer thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of selectively modulating a PPAR delta receptor by

contacting the receptor with at least one compound represented by Structural Formula I, or a pharmaceutically acceptable salt, solvate, hydrate, or stereioisomer thereof.

In another embodiment, the present invention relates to a method of modulating one or more of the PPAR alpha, beta, gamma, and/or delta receptors.

In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention are believed to be effective in treating and preventing Metabolic Disorder, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, atherosclerosis, and other disorders related to Metabolic Disorder and cardiovascular diseases. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease. In addition, the compounds can be associated with fewer clinical side effects than compounds currently used to treat such conditions.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings.

As used herein, the term "aliphatic linker" or "aliphatic group" is a non-aromatic, consisting solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An

aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatics are preferably C_1-C_{10} straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C_1-C_6 straight chained or branched alkyl groups. Examples include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclohexylyl and the like. Such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30. It can be preferred that aliphatic linker is substituted with from zero to two substituents each independently selected from R30. Further, it may be preferred that one carbon of the alphatic linker is replaced with an O, NH, or S.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated

configuration. As used herein, "C_0 alkyl" means that there is no carbon and therefore represents a bond. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. As used herein, the term "alkyloxo" means an alkyl group of the designated number of carbon atoms with a "=O" substituent.

The term "alkenyl" or "alkylenyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like. Alkenyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "heteroalkyl" refers to a means hydrocarbon chain of a specified number of carbon atoms wherein at least one carbon is replaced by a heteroatom selected from the group consisting of O, N and S.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, typically 3 to 7 carbon atoms.

Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. "Cycloalkyaryl" means that an aryl is fused with a cycloalkyl, and "Cycloalkylaryl-alkyl" means that the cycloalkylaryl is linked to the parent molecule through the alkyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl (CF_3).

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "haloalkyloxy" represents a C_1-C_6 haloalkyl group attached through an oxygen bridge, such as OCF_3. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above

may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "arylalkyl" refers to an aryl alkyl group which is linked to the parent molecule through the alkyl group, which may be further optionally substituted with a designated number of substituents as set forth in the embodiment recited above. When arylalkyl is arylC_0alkyl, then the aryl group is bonded directly to the parent molecule. Likewise, arylheteroalkyl means an aryl group linked to the parent molecule through the heteroalkyl group.

The term "acyl" refers to alkylcarbonyl species.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from the group consisting of O, N, and S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, indolyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazoyl, oxazoyl, pyrazoyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like. The term "heteroarylalkyl" means that the heteroaryl group is linked to the parent molecule through the alkyl portion of the heteroarylalkyl.

The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-

aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. As used herein, alkyl groups include straight chained and branched hydrocarbons, which are completely saturated.

As used herein, the phrase "selectively modulate" means a compound whose EC50 for the stated PPAR receptor is at least ten fold lower than its EC50 for the other PPAR receptor subtypes.

PPARδ has been proposed to associate with and dissociate from selective co-repressors (BCL-6) that control basal and stimulated anti-inflammatory activities (Lee, C-H. et al. Science 302:453-4572003). PPARδ agonists are thought to be useful to attenuate other inflammatory conditions such as inflammation of the joints and connective tissue as occurs in rheumatoid arthritis, related autoimmune diseases, osteroarthritis, as well as myriad other inflammatory diseases, Crohne's disease, and psoriasis.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are considered to be acceptable for clinical and/or veterinary use. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid additiona salts and base addition salts, respectively. It will be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. These salts may be prepared by methods known to the skilled artisan.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the sterioisomers, salts, solvates, and hydrates,

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt are pharmaceutically compatible with the other ingredients of the composition.

Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term "preventing" is particularly applicable to a patient that is susceptible to the particular patholical condition.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of active ingredientit, that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a selected PPAR receptor or to prevent or mediate a disease or condition. Generally, the effective amount of a Compound of Formula I will be between 0.02 through 5000 mg per day. Preferably the effective amount is between 1 through 1,500 mg per day. Preferably the dosage is from 1 through 1,000 mg per day. A most preferable the dose can be from 1 through 100 mg per day.

The desired dose may be presented in a single dose or as divisded doses administered at appropriate intervals.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes

humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors for the development of heart disease, stroke, and circulatory system disorders and diseases.

Further, the compound and compositions of the present invention may reduce the incidence of undesired cardiac events in patients. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body weight gains by the patients. Furthermore, the compounds and compositions of the present invention are useful to treat or prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or

non-human mammal which comprises administering an effective amount of active ingredient, as defined herein, to a hyperglycemic human or non-human mammal in need thereof.

The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPAR receptor mediated condition.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Metabolic Disorder, diabetes, treating obesity, lowering tryglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more. In adition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about 0.7% or more.

When used herein Metabolic Syndrome includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any

combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis. In addition, the methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following inflammatory and autoimmune diseases: adult respritory distress syndrome, rheumatoid arthritis, demyelinating disease, Chrohne's disease, asthma, systemic lupus erythematosus, psoriasis, and bursitis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I, a stereoisomer, salt, solvate and/or hydrate thereof ("Active Igredient") and one or more additional active agents, as well as administration of a compound of Active Ingredient and each active agent in its own separate pharmaceutical dosage formulation. For example, an Active Ingredient and an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, an Active Ingredient and one or more additional active agents can be administered at essentially the same time,

i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein an Active Ingredient is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the Active Ingredient can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the Active Ingredient can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The Active Ingredients of the present invention, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of Active Ingredient of the present invention, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the Active Ingredient of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the Active Ingredient of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1500 milligrams or more according to the particular treatment involved. It may be preferred that the unit dosage is from about 1 mg to about 1000 mg.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

Solid form formulations include powders, tablets and capsules.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The following pharmaceutical formulations 1 and 2 are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg .

In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new selective PPAR receptor agonists.

The compounds of the present invention can be useful for modulating insulin secretion and as research

tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

Some prefered characteristics of compounds of formula I are:

(a) R3 is methyl;
(b) R4 is hydrogen;
(c) R3 and R4 are each hydrogen;
(d) R3 and R4 are each methyl;
(e) A is carboxyl;
(f) X is -O-;
(g) X is -S-;
(h) U is CH;
(i) U is CH_2CH;
(j) R9 is methyl;
(k) R9 is hydrogen;
(l) R9 is C_1-C_3 alkyl;
(m) R8 is methyl;
(n) R8 and R9 are each hydrogen;
(o) R10 is CF_3;
(p) R10 is haloalkyl;
(q) R10 is haloalkyloxy;
(r) R11 is hydrogen
(s) R10 and R11 are each hydrogen;
(t) R11 is haloalkyl;
(u) Z3 is N;
(v) Z2 and Z3 are each N;
(w) Z1 and Z3 are each N;

(x) Z3 is O;

(y) R1 is optionally substituted C2-C3 arylalkyl;

(z) R1 is substituted C2 arylalkyl;

(aa) R2 is bonded to Z3;

(bb) Z1 is N;

(cc) Z3 is O;

(dd) Z1, Z2, and Z3 are each N;

(ee) Z1 and Z3 are each N and Z2 is C;

(ff) R2 is bonded to Z2;

(gg) Z1 is O, Z2 is N and Z3 is C;

(hh) R2 is bonded to Z3;

(ii) Z1 and Z3 are each N;

(jj) ---- in the five membered ring each form a double bond at the designated position in Formula I;

(kk) R1 is C_1-C_4 alkyl;

(ll) R32 is hydrogen;

(mm) R2 is a bond;

(nn) R2 is C_1-C_2 alkyl;

(oo) Y is O;

(pp) Y is S;

(qq) Y is C;

(rr) Y is C, NH, or a bond;

(ss) E is C(R3)(R4)A;

(tt) R3 is hydrogen;

(uu) R3 is C_1-C_2 alkyl;

(vv) R4 is C_1-C_2 alkyl;

(ww) R3 and R4 are each hydrogen;

(xx) R3 and R4 are each methyl;

(yy) A is COOH;

(zz) Aliphatic linker is saturated;

(aaa) Aliphatic linker is substituted with C_1-C_3 alkyl;

(bbb) Aliphatic linker is substituted with from one to three substituents each independently selected from R30;

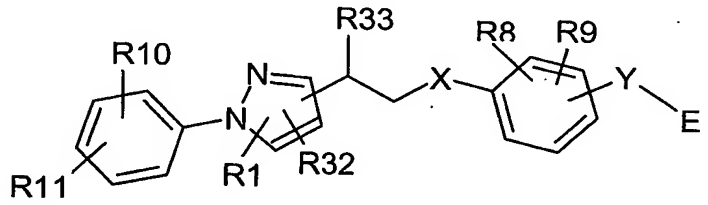
(ccc) Aliphatic linker is substituted with from one to two substituents each independently selected from R30;

(ddd) Aliphatic linker is C_1-C_3 alkyl;

(eee) Aliphatic linker is C_1-C_2 alkyl;

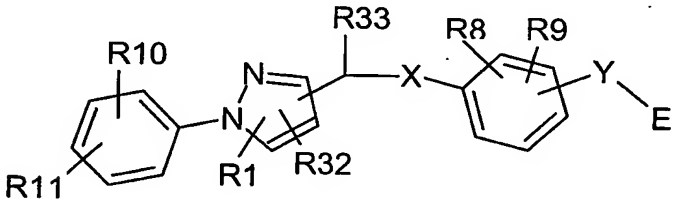
(fff) Aliphatic linker is C_1-C_3 alkyl and one carbon is replaced with an -O-;

(ggg) A compound of Formula II:



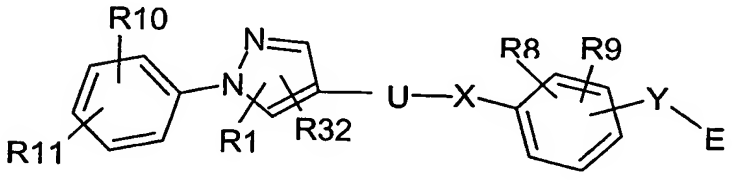
;

(hhh) A compound of Formula III:



;

(iii) A compound of Formula IV:

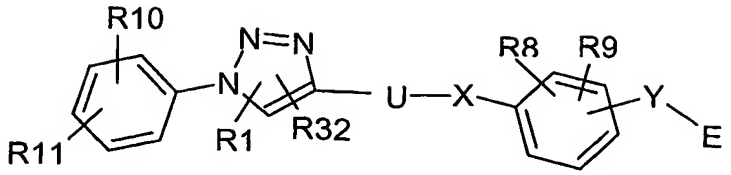


;

(jjj) Aryl is a phenyl group;

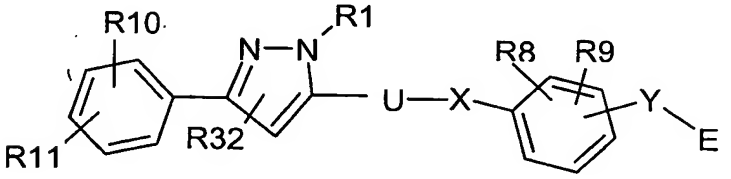
(kkk) Aryl is a naphthyl group;

(lll) A compound of Formula I that is:



;

(mmm) A compound of Formula I that is



;

(nnn) A compound of Formula I that selectively modulates a delta receptor;

(ooo) An Active Ingredient, as described herein, that is a PPAR coagaonist that modulates a gamma receptor and a delta receptor;

(ppp) An Active Ingredient, as described herein, for use in the treatment of cardiovascular disease;

(qqq) An Active Ingredient, as described herein, for use in the treatment of Metabolic Disorder;

(rrr) An Active Ingredient for use in the control of obesity;

(sss) An Active Ingredient for use in treating diabetes;

(ttt) An Active Ingredient that is a PPAR receptor agonist;

(uuu) A compound of Formula I selected from the group consisting of

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid;

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid;

{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid;

(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid;

2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid;

3-(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;

{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid;

{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-phenoxy}-acetic acid;

3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid;

3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid;

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenoxy}-acetic acid; and

3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

(iii) A compound of Formula I selected from the group consisting of (R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid, and (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid; and

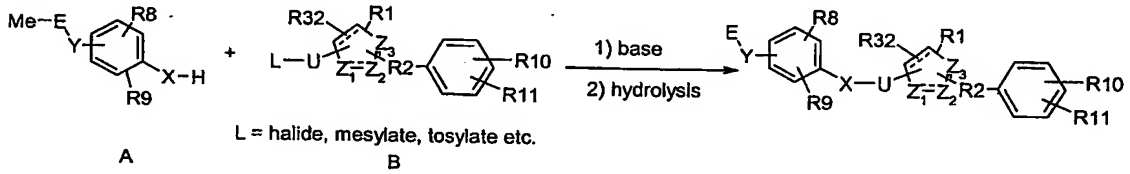
(jjj) A compound of Formula I that is (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid.

SYNTHESIS

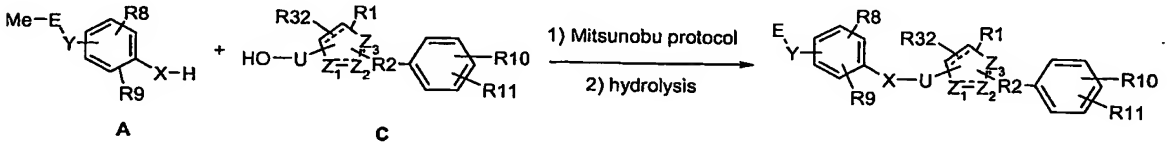
Compounds of the present invention have been formed as specifically described in the examples. Further, many

compounds are prepared as more generally using a) alkylation of phenol/thiophenol with a halide, b) a Mitsunobu protocol (O. Mitsunobu, 1981 Synthesis, p1); c) and other methods known to the skilled artisan. Alternative synthesis methods may also be effective and known to the skilled artisan.

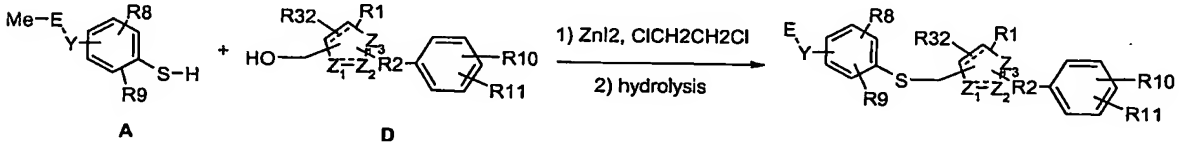
For example, an intermediate like A is alkylated with an alkylating agent B in the presence of a base (e.g. K2CO3, Cs2CO3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product.



Alternatively, an intermediate like A is coupled with an alcohol C under Mitsunobu reaction condition (DEAD/PPh3, ADDP/Pbu3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product:

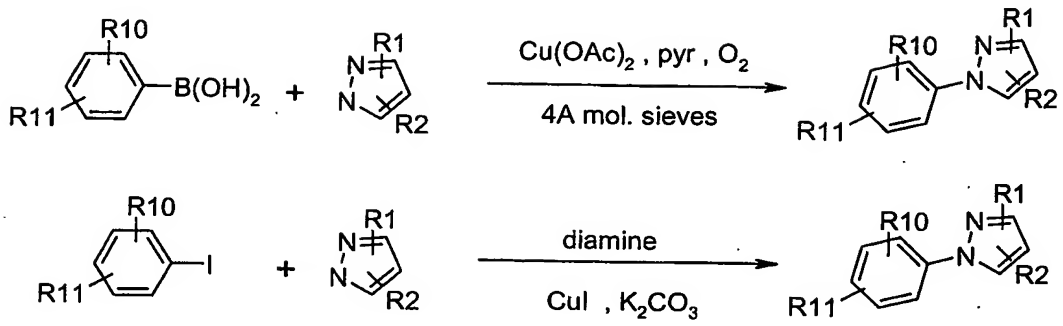


Thioether analogs could also be prepared by a ZnI2 mediated thioether formation reaction as shown below:



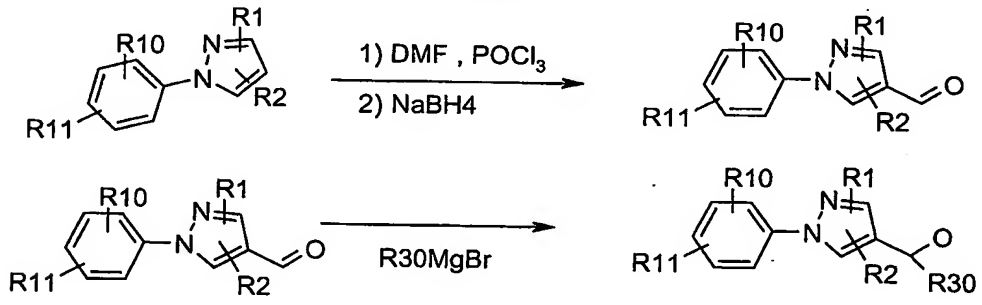
Intermediates B, C and D can be made in one of the following methods. Coupling reaction between pyrazole and aryl boronic acid or Aryl halide in the presence of copper gave the 1-arylpyrazole:

Scheme 1



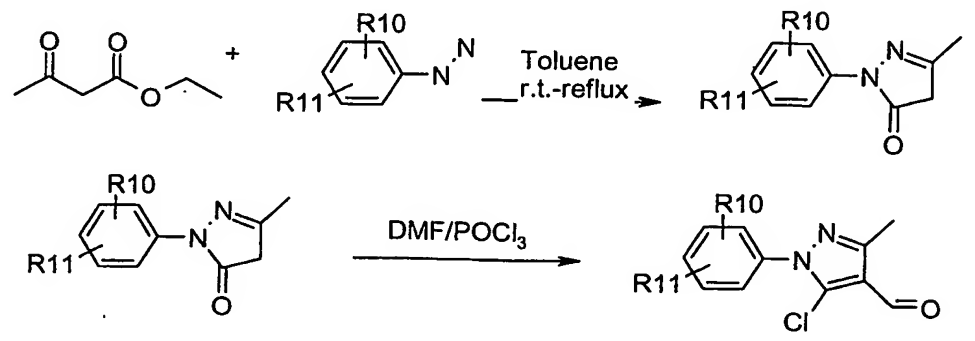
Formylation under Vilsmeier-Haack reaction condition of the 3-arylpyrazole gave the 3-formyl pyrazole, sodium borohydride reduction afforded the primary alcohol. The secondary alcohol intermediates can be obtained by alkylation with a Grignard reagent.

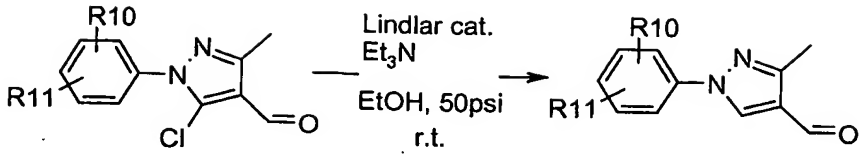
Scheme 2



Alternatively, the pyrazole intermediates can be made by the following method starting from β-ketoesters:

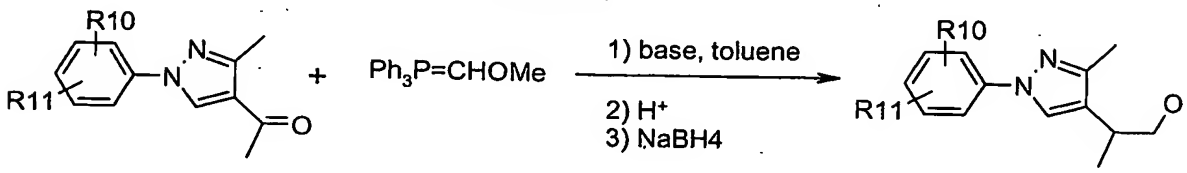
Scheme 3





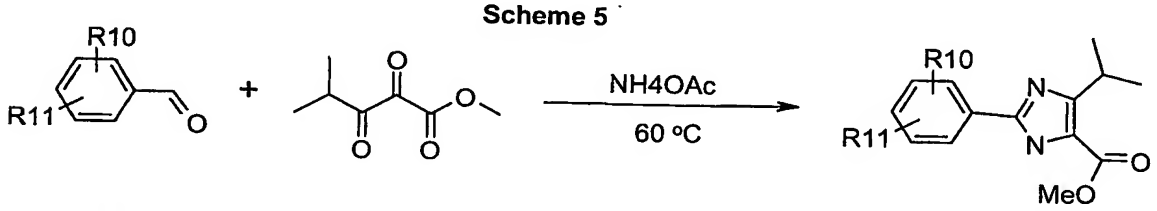
A Wittig reaction is used to extend chain at 4-position as shown in scheme 4:

Scheme 4



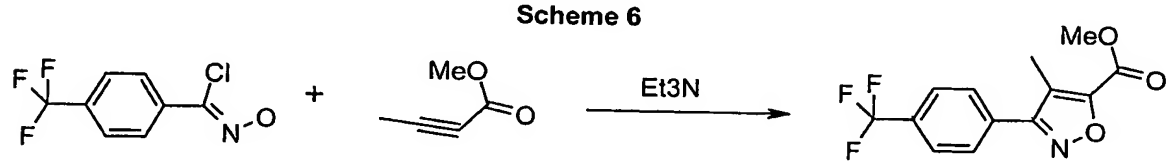
Imidazole intermediate can be made according to scheme 5:

Scheme 5



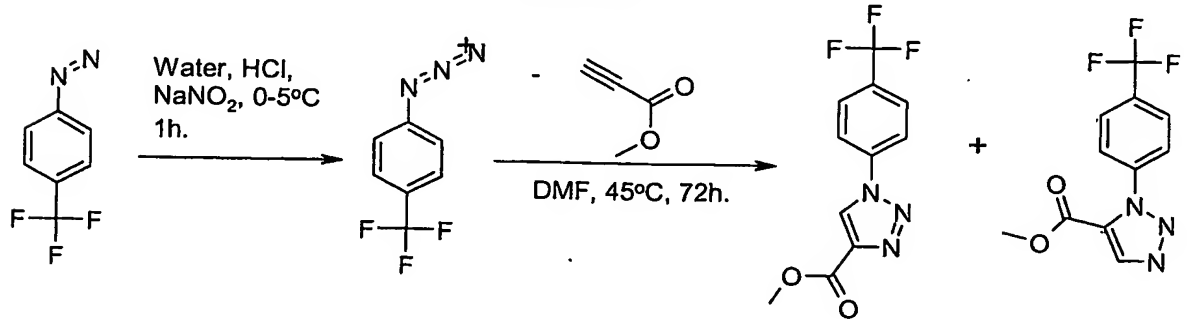
Isoxazole intermediate is obtained by the following cycloaddition reaction:

Scheme 6



Triazole intermediate can be made by the following method:

Scheme 7



EXEMPLIFICATION

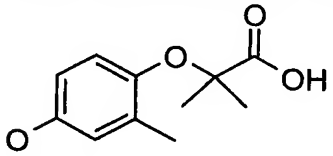
The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way.

Instrumental Analysis

Infrared spectra are recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR spectra are recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR are recorded on a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Combustion analyses are performed by Eli Lilly & Company Microanalytical Laboratory. High resolution mass spectra are obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography is performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization is accomplished with UV light.

Preparation 1

2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid



Step A

2-(4-Benzyloxy-2-formylphenoxy)-2-methyl propionic acid ethyl ester

5-Benzyloxy-2-hydroxy-benzaldehyde (Kappe, T.; Witoszynskyj, T. Arch. Pharm., 1975, 308 (5), 339-346) (2.28 g, 10.0

mmol), ethyl bromoisobutyrate (2.2 mL, 15 mmol), and cesium carbonate (3.26 g, 10.0 mmol) in dry DMF (25 mL) are heated at 80 °C for 18 h. The reaction mixture is cooled and partitioned between water (30 mL) and ether (75 mL). The organic layer is washed with brine (15 mL). The aqueous layers are back-extracted with ethyl acetate (30 mL), and the organic layer is washed with brine (20 mL). The combined organic layers are dried (Na_2SO_4) and concentrated to a brown oil. The crude product is purified by flash chromatography using hexanes:ethyl acetate (2.5:1) to give a pale yellow solid (3.04 g, 89%): mp 65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz), 1.62 (s, 6H), 4.23 (q, 2H, J = 7.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 4.6, 9.0 Hz), 7.30-7.43 (m, 6H); MS (ES) m/e 343.1 [M+1].

Step B

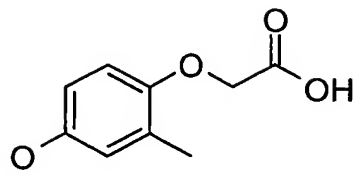
2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester

2-(4-Benzyloxy-2-formyl-phenoxy)-2-methyl-propionic acid ethyl ester (9.00 g, 26.3 mmol) in ethanol (250 mL) is treated with 5% Pd/C (1.25 g) and hydrogen (60 psi, rt, overnight). Additional 5% Pd/C (1.25 g) is added, and the reaction is continued for 6h at 40 °C. The mixture is filtered and concentrated to a tan oil (6.25 g). This oil contained 9 mol% of 2-(4-Hydroxy-2-hydroxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 1.51 (s, 6H), 2.14 (s, 3H), 4.24 (q, 2H, J = 7.3 Hz), 5.68 (brs, 1H), 6.47 (dd, 1H, J = 3.4, 8.8 Hz), 6.59 (d, 1H, J = 8.3 Hz), 6.60 (brs, 1H).

The following compound is prepared in a similar manner:

Preparation 2

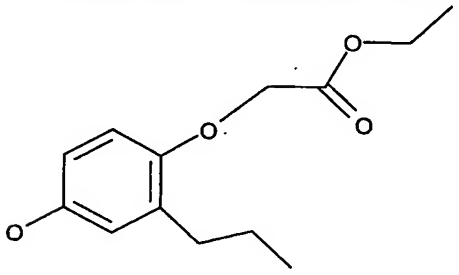
2-(4-Hydroxy-2-methyl-phenoxy)-acetic acid



^{1}H NMR (400 MHz, CDCl3) δ 1.28 (t, 3H, J = 7.1 Hz), 2.24 (s, 3H), 4.25 (q, 2H, J = 7.1 Hz), 4.55 (s, 2H), 6.56 (dd, 1H, J = 2.7, 8.5 Hz), 6.61 (d, 1H, J = 8.3 Hz), 6.65 (d, 2H, J = 2.9 Hz).

Preparation 3

(4-Hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester



Step A

4-Benzyloxy-2-propylphenol

2-Allyl-4-benzyloxyphenol (WO 9728137 A1 19970807, Adams, A.D. et al.) (5.00 g, 20.8 mmol) in ethyl acetate (40 mL) is treated with 5% Pd/C (0.25 g) and hydrogen (1 atm) at ambient temperature for 18 h. The mixture is filtered and concentrated. The crude product is purified on a Biotage medium pressure chromatography system using a 40L normal phase cartridge and eluted with 10% ethyl acetate in hexanes to give a tan solid (2.8 g, 56%). Rf = 0.33 (25% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.78 (s, 1H), 6.69 (d, J = 1.5 Hz, 2H), 5.00 (s, 2H), 4.31 (s, 1H), 2.55 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

Step B

(4-Benzyloxy-2-propylphenoxy)acetic acid ethyl ester

A solution of 4-benzyloxy-2-propylphenol (0.50 g, 1.94 mmol) in dry DMF (7 mL) is cooled in an ice bath and treated with NaH (0.15 g, 3.8 mmol, 60 % oil dispersion). The ice bath is removed, ethyl bromoacetate (0.43 mL, 3.9 mmol) is added, and the mixture is placed in an oil bath (T=85 °C). After 18 h, the reaction mixture is cooled and concentrated in vacuo. The residue is diluted with EtOAc, washed with brine (2x), dried (Na_2SO_4), and concentrated. The crude product is purified by radial chromatography using 10% ethyl acetate in hexanes to give a tan solid (0.62 g, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.82 (d, J = 2.9 Hz, 1H), 6.72 (dd, J = 8.8, 2.9 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.00 (s, 2H), 4.57 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 329 (M+1).

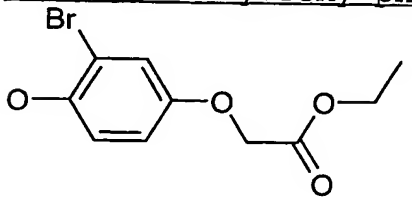
Step C

(4-Hydroxy-2-propylphenoxy)acetic acid ethyl ester

A solution of (4-benzyloxy-2-propylphenoxy)acetic acid ethyl ester (0.60 g, 1.83 mmol) in THF (15 mL) is treated with 5% Pd/C (75 mg) and hydrogen (60 psi) at ambient temperature for 24 h. The mixture is filtered and concentrated. The crude product is purified by radial chromatography using 15% ethyl acetate in hexanes to give a tan solid (0.25 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.9 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.9 Hz, 1H), 4.56 (s, 1H), 4.40 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.63 (q, J = 7.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 239 (M+1).

Preparation 4

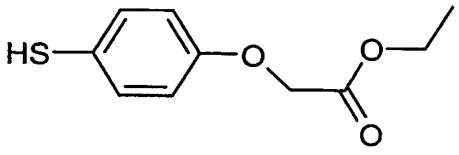
(3-Bromo-4-hydroxy-phenoxy)-acetic acid ethyl ester



To a solution of (4-hydroxy-phenoxy)-acetic acid ethyl ester (0.59 g, 3 mmol) in acetic acid (1.5 mL) is added bromine (0.48 g, 9 mmol) in acetic acid (0.5 mL) at room temperature. After 5 min, solvent is evaporated and purified by column chromatography on silica gel giving the title compound (0.6 g).

Preparation 5

(4-Mercapto-phenoxy)-acetic acid ethyl ester



Step A

(4-Chlorosulfonyl-phenoxy)-acetic acid ethyl ester

Phenoxy-acetic acid ethyl ester (9.1 mL) is added to chlorosulfonic acid (15 mL) at 0°C dropwise. The reaction is stirred at 0 °C for 30 min, it is allowed to warm to room temperature. After 2 hrs, the reaction mixture is poured into ice, solid product is collected by filtration and dried under vacuum.

Step B

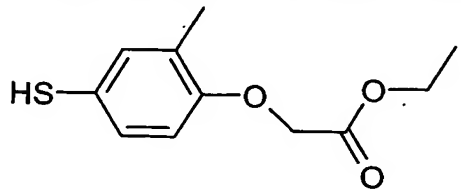
(4-Mercapto-phenoxy)-acetic acid ethyl ester

To a mixture of (4-chlorosulfonyl-phenoxy)-acetic acid ethyl ester (0.98 g, 3.5 mmol) and tin powder (2.1 g) in ethanol (4.4 mL) is added HCl in dioxane (1.0 M, 4.4 mL) under nitrogen. The mixture is heated to reflux for 2 hrs, it is poured into ice and methylene chloride and filtered. The layers are separated and extracted with methylene chloride, dried and concentrated. The crude product is used for next step without purification.

The following compounds are made in a similar manner:

Preparation 6

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester

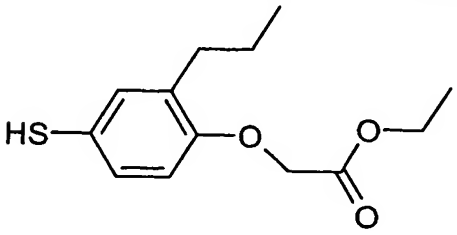


This compound can also be made by the following procedure: To a stirred suspension of Zn powder (10 μm, 78.16 g, 1.2 mol) and dichlorodimethyl silane (154.30 g, 145.02 mL, 1.2 mol) in 500 mL of dichloroethane is added a solution of (4-chlorosulfonyl-2-methyl-phenoxy)-acetic acid ethyl ester (100 g, .34 mol) and 1,3-dimethylimidazolidin-2-one (116.98 g, 112.05 mL, 1.02 mol) in 1L of DCE. Addition is at a rate so as to maintain the internal temperature at ~ 52 °C, cooling with chilled water as necessary. After addition is complete, the mixture is heated at 75 °C for 1 hour. It is then cooled to room temperature, filtered and concentrated *iv*. Add MTBE, washed twice with saturated LiCl solution , concentrate *iv* again. Take up the residue in CH_3CN, wash with hexane (4X) and concentrate *iv* to yield a biphasic mixture. Let stand in a separatory funnel and separate layers, keeping the bottom layer for product. Filtration through a plug of silica gel (1 Kg, 25% EtOAc/hexane) and subsequent concentration yields 61 g (79%) of a clear, colorless oil.

NMR (DMSO-d_6) δ 7.1 (s, 1H), 7.05 (dd, 1H), 6.75 (d, 1H), 5.03 (s, 1H), 4.75 (s, 2H), 4.15 (q, 2H), 2.15 (s, 3H), 1.2 (t, 3H).

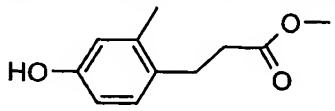
Preparation 7

(4-Mercapto-2-propyl-phenoxy)-acetic acid ethyl ester



Preparation 8

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester



Step A

4-Bromo-3-methyl-phenyl benzyl ester

To a solution of 4-Bromo-3-methyl-phenol (20.6 g, 0.0.11 mol) in DMF (100 mL) is added Cs2CO3 (54 g, 0.165 mol), followed by benzyl bromide (14.4 mL). After stirred at 60 °C for 40 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is washed with water and brine, dried over sodium sulfate, concentration yields the title product (27 g).

Step B

3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 4-bromo-3-methyl-phenyl benzyl ester (7.6 g, 27.4 mmol) in propronitrile (200 mL) is added methyl acrylate (10 mL) and diisopropylethyl amine (9.75 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (3.36 g) and palladium acetate (1.25 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate yields the title compound (6.33 g).

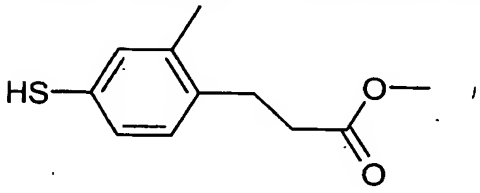
Step C

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester (13.7 g, 48.5 mmol) and Pd/C (5 %, 13.7 g) in MeOH (423 mL) is stirred under 60 psi of hydrogen for 24 hrs. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.8 g, 93.5%).

Preparation 9

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (5.0 g, 25.75 mmol) is dissolved into dry dioxane (100 mL) and combined with 4-dimethylamino pyridine (0.500 g, 2.6 mmol), triethylamine (7.0 mL, 51.5 mmol), and dimethylaminothiocarbomoyl chloride (4.5 g, 32.17 mmol). The reaction is heated to reflux under nitrogen. The reaction is monitored by TLC until all of the phenol is consumed, 20h. After cooling to room temperature, the reaction is diluted with ethyl acetate (200 mL). Water (75 mL) is added and the two layers are separated. The organic layer is washed with brine (75mL) then dried over anhydrous sodium sulfate. The solvent is removed and the residue is dried under vacuum.

Step B

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester, taken crude from the previous step, is diluted with 75 mL of tetradecane and heated to reflux under nitrogen. The reaction is monitored by TLC until all the

conversion is complete, 20h. The reaction is allowed to cool to room temperature, then the tetradecane is decanted away from the resulting oil. The residue is rinsed several times with hexanes. This oil is then purified using flash column chromatography, yielding 5.01 g, or 69% (2 steps) of the product.

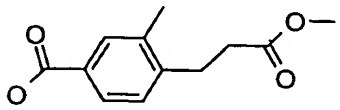
Step C

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester (5.01 g, 17.8 mmol) is diluted with methanol (30 mL) and to this is added sodium methoxide (1.7 mL of 4M in methanol, 7.23 mmol). The reaction is heated to reflux under nitrogen and monitored by TLC. After complete conversion, 20h., the reaction is allowed to cool to room temperature. The reaction is neutralized with 1N HCl (7.23 mL) and diluted with ethyl acetate (150 mL). The two phases are separated and the organic layer is washed with water (75 mL), then brine (75 mL). The organic layer is then dried over anhydrous sodium sulfate, then concentrated to yield 4.43 g crude product that is used without further purification.

Preparation 10

4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid



Step A

4-Bromo-3-methyl-benzoic acid benzyl ester

To a solution of 4-Bromo-3-methyl-benzoic acid benzyl (25.3 g, 0.118 mol) in DMF (200 mL) is added Cs_2CO_3 (76.6 g, 0.235 mol), followed by benzyl bromide (15.4 mL). After stirred at room temperature for 2 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is

washed with water and brine, dried over sodium sulfate, concentration yields the title product.

Step B

4-(2-Methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester

To a solution of 4-bromo-3-methyl-benzoic acid benzyl ester (36 g, 118 mmol) in propronitrile (1000 mL) is added methyl acrylate (43.3 mL) and diisopropylethyl amine (42 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (14.5 g) and palladium acetate (5.34 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate yields the title compound (31 g, 84.7%).

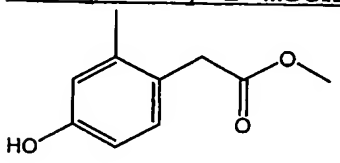
Step C

4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid

A mixture of 4-(2-methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester (11.6 g, 37.4 mmol) and Pd/C (5 %, 1.5 g) in THF (300 mL) and methanol (100 mL) is stirred under 60 psi of hydrogen overnight. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.3 g, 100%).

Preparation 11

(4-Hydroxy-2-methyl-phenyl)-acetic acid methyl ester



Step A

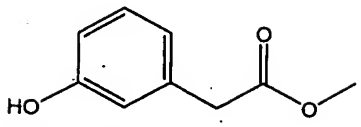
4-Methoxy-2-methylbenzoic acid (2.5 g, 15.04 mmol) is stirred in thionyl chloride (50 mL) at reflux 2 hr. The mixture is concentrated and diluted with toluene (10 mL) and concentrated. The resulting solid is dried under vacuum 18 hr. The resulting acid chloride is stirred in 20 mL ether at 0 deg C. A solution of diazomethane (39.6 mmol) in ether (150 mL) is added to the acid chloride solution and stirred 18 hr. The resulting diazoketone solution is concentrated. The residue is stirred in methanol (100 mL) and a solution of silver benzoate in triethylamine (1.0 g in 10 mL) is added and the reaction is heated to 60 deg C and stirred 1 hr. The mixture is concentrated, diluted with 1.0 N aqueous hydrochloric acid (20 mL), extracted to three portions of ethyl acetate (50 mL each). The extracts are combined, washed with aqueous saturated sodium hydrogen carbonate, water, and brine (50 mL each), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified via silica gel chromatography eluting with 9:1 hexanes:ethyl acetate to afford 1.5 g (51%) of the homologated ester as a white solid.

Step B

(4-Methoxy-2-methyl-phenyl)-acetic acid methyl ester (1.5 g, 7.72 mmol) is stirred in dichloromethane (50 mL) at 0 deg. C. Aluminum chloride (4.13 g, 31 mmol) is added followed by ethane thiol (2.9 mL, 38.6 mmol) . The resulting mixture is stirred at room temperature for 2 hr. Water (50 mL) is added and the product is extracted into ethyl acetate (3 X 50 ml), the extracts are combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford the title compound as a colorless oil, 1.4 g, 100%. MS M^++1 181. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 12

(3-Hydroxy-phenyl)-acetic acid methyl ester



Step A

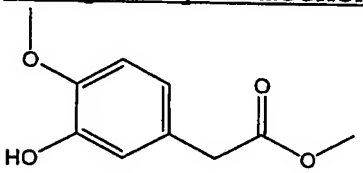
(3-Hydroxy-phenyl)-acetic acid methyl ester

(3-Hydroxy-phenyl)-acetic acid (5.0 g, 32.86 mmol) is stirred in methanol (100 mL) and concentrated (98%) sulfuric acid (3.0 mL,) is added. The mixture is heated to reflux 18 hr. The reaction is cooled and concentrated. The residue is diluted with water (100 mL) and extracted with ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the title compound as an orange oil, 5.46 g, 100%. MS M^++1 167. The structure is confirmed by ^{1}H NMR spectroscopy.

The following compounds are made in a similar manner:

Preparation 13

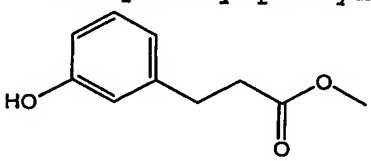
(3-Hydroxy-4-methoxy-phenyl)-acetic acid methyl ester



An orange oil. MS M^++1 197. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 14

3-(3-Hydroxy-phenyl)-propionic acid methyl ester



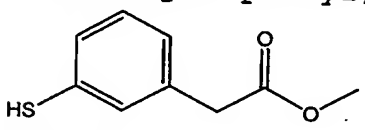
Step A

3-(3-Hydroxy-phenyl)-propionic acid methyl ester

An orange oil. MS M^++1 181. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 15

(3-Mercapto-phenyl)-acetic acid methyl ester



Step A

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester

A mixture of (3-Hydroxy-phenyl)-acetic acid methyl ester (5.5 g, 33.1 mmol) , N,N-dimethyl thiocarbamoyl chloride (5.11 g, 41.38 mmol), triethylamine (9.2 mL, 66.2 mmol), N,N-dimethylamino pyridine (0.4 g, 3.31 mmol) and dioxane (50 mL) is stirred at reflux 18 hr. The mixture is concentrated, partioned between 1M aqueous hydrochloric acid (200 mL) and ethyl acetate (3 X 75 mL). The combined organic extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting the product with dichloromethane to afford the title compound as a brown oil, 6.8 g, 81%. MS M^++1 254. The structure is confirmed by ^{1}H NMR spectroscopy.

Step B

(3-Dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester (6.8 g, 26.84 mmol) is stirred in tetradecane (30 mL) at 255 deg C for 8 hr. The mixture is cooled, the residue is purified by silica chromatography eluting the product with hexanes to 1:1 hexanes:ethyl acetate to afford the title compound as an orange oil, 4.9 g, 58 %. MS M^++1 254. The structure is confirmed by ^{1}H NMR spectroscopy.

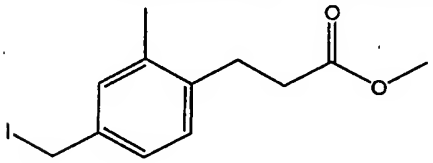
Step C

(3-Mercapto-phenyl)-acetic acid methyl ester

A mixture of (3-dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester (2.0 g, 7.9 mmol), potassium hydroxide (1.4 g, 24 mmol) methanol (50 mL), and water (5 mL) is stirred at reflux 3 hr. The mixture is concentrated, and product partitioned between 1M aqueous hydrochloric acid (50 mL) and ethyl acetate (3 X 75 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is taken up in methanol (50 mL), 2 mL concentrated sulfuric acid is added, and the mixture refluxed 3 hr. The mixture is concentrated, and the residue purified by silica chromatography eluting with 7:3 hexanes:ethyl acetate to afford the title compound as a pale yellow oil, 1.0 g, 69%. MS M^++1 183. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 16

3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester

A mixture of methyl-4-bromo-3-methylbenzoate (5.7 g, 24.88 mmol), lithium aluminum hydride (29 mL, 29 mmol, 1 M solution in tetrahydrofuran) and tetrahydrofuran (100 mL) is stirred in ice/water for 1 hr. The reaction is quenched with aqueous hydrochloric acid (50 mL, 1 M). The product is extracted into ethyl acetate (3 X 100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product is taken up in propionitrile (100 mL). Methylacrylate (10 mL, 121.5 mmol), palladium acetate (1.12 g, 5 mmol), tri-o-tolylphosphine (3.0 g, 10 mmol), and N,N-diisopropyl ethylamine (8.7 mL, 50 mmol) are sequentially added and the resulting reaction

mixture is heated to 110 deg C 3 hr. The mixture is concentrated, and the residue diluted with aqueous hydrochloric acid (100 mL, 1M).The product is extracted with dichloromethane (2 X 100 mL) and ethyl acetate (100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting with 7:3 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate to afford the pure product as a yellow oil, 4.7 g, 91 %. MS M^++1 207. The structure is confirmed by ^{1}H NMR spectroscopy.

Step B

3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester (4.7 g, 22.8 mmol), Raney nickel (0.668 g) and tetrahydrofuran (618 mL) is shaken under 60 psig. Hydrogen 24 hr. The catalyst is filtered off, and the mixture is concentrated to afford the product as a pale yellow oil, 4.3 g, 91%. The structure is confirmed by ^{1}H NMR spectroscopy.

Step C

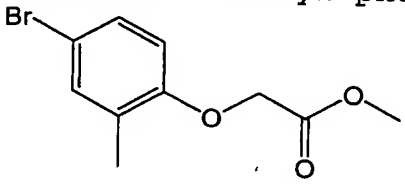
3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.62 g, 2.98 mmol), triphenyl phosphine (0.86 g, 3.27 mmol) and dichloromethane (10 mL) is stirred at room temperature. A solution of iodine (0.83 g, 3.27 mmol) in benzene (5 mL) is added and the black mixture is stirred at room temperature 2hr. The brown mixture is diluted with 10% aqueous sodium hydrogen sulfite (5 mL) and the resulting clear mixture is washed with ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue

is purified via silica chromatography eluting with 9:1 hexanes:ethyl acetate to afford the title compound as a crystalline ivory solid, 0.68g, 72%. MS M^++1 319. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 17

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester



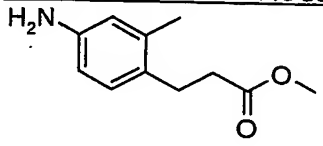
Step A

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester

A mixture of 4-bromo-2-methylphenol (1.0 g, 5.35 mmol), sodium hydride (0.26 g, 6.42 mmol, 60% mineral oil), N,N-dimethylformamide (10 mL), and methyl-2-bromoacetate (0.56 mL, 5.88 mmol) is stirred at room temperature 18 hr. The mixture is diluted with water (50 mL) and the product extracted to ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated and purified via silica chromatography eluting with 8:2 hexanes:ethyl acetate to afford title compound as a colorless oil, 1.03 g, 74%. MS M^+ 259. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 18

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester

To a solution of 2-bromo-5-nitrotoluene (3.11 g, 14.39 mmol) in propionitrile (105 mL) is added DIPEA (5.1 mL, 29.28 mmol). The mixture is degassed three times. Methyl acrylate (5.2 mL, 57.74 mmol) is added and the mixture is

degassed. Tri-*o*-tolylphosphine (1.77 g, 5.82 mmol) and $Pd(OAc)_2$ (0.64 g, 2.85 mmol) are added and the mixture is degassed a final two times followed by heating at 110°C for 4 h. Upon cooling, the mixture is passed through Celite and the filtrate is concentrated. The residue is partitioned between Et_2O and 1N HCl. The organics are washed with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. The crude material is purified by flash chromatography to yield the title compound (2.90 g, 91%).

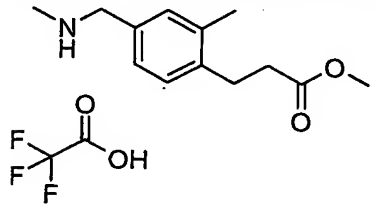
Step B

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester (1.47 g, 6.64 mmol) and 5% Pd/C (0.29 g) in MeOH (100 mL) is exposed to a hydrogen atmosphere (60 psi) for 12 h. The mixture is filtered through Celite and purified by flash chromatography to yield the title compound (0.99 g, 77%).

Preparation 19

3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester TFA salt



Step A

3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.49 g, 2.35 mmol) and MnO_2 (0.80 g, 9.20 mmol) in chloroform (5 mL) is stirred at RT for 4 days. The mixture is filtered through Celite; the Celite is washed with copious amounts of EtOAc. The filtrate is concentrated and purified by flash chromatography to yield the title compound (0.29 g, 60%).

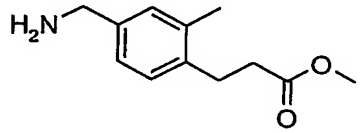
Step B

3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester trifluoroacetic acid

To a mixture of 3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester (0.27 g, 1.31 mmol) and methylamine (2M in THF, 0.60 mL, 1.20 mmol) in anhydrous CH_2Cl_2 (10 mL) is added 4Å molecular sieves followed by acetic acid (0.090 mL, 1.57 mmol). The mixture is stirred at RT for 1.5 h. Sodium triacetoxyborohydride (0.39 g, 1.85 mmol) is added, and the mixture is stirred overnight. The reaction is quenched with saturated $NaHCO_3$. The organics are washed with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Upon concentration, the mixture is purified by reverse phase chromatography to yield the title compound (0.12 g, 45%).

Preparation 20

3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester

To a 0°C solution of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (1.02 g, 4.90 mmol) in anhydrous CH_2Cl_2 (15 mL) is added triethylamine (0.75 mL, 5.38 mmol) followed by thionyl chloride (0.40 mL, 5.48 mmol). The mixture is allowed to warm to RT overnight. Water is added, and the mixture is extracted with CH_2Cl_2. The organics are dried with $MgSO_4$ and concentrated. The crude material is purified by flash chromatography to yield the title compound (1.01 g, 91%).

Step B

3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester (0.52 g, 2.31 mmol) in DMF (7 mL) is added sodium azide (0.25 g, 3.84 mmol). The mixture is stirred overnight. Water is added, and the mixture is extracted with EtOAc. The organics are dried with Na_2SO_4 and concentrated to yield the title compound (0.49 g, 91%). The material is used without further purification.

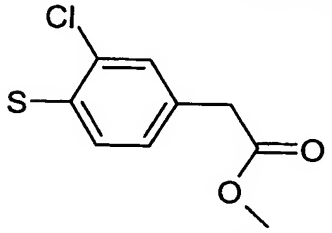
Step C

3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester (0.20 g, 0.86 mmol) and 5% Pd/C (32 mg) in EtOH (50 mL) is exposed to a hydrogen atmosphere (60 psi) at RT overnight. Upon filtering the mixture through Celite, the filtrate is concentrated to yield the title compound (0.14 g, 78%). The material is used without further purification.

Preparation 21

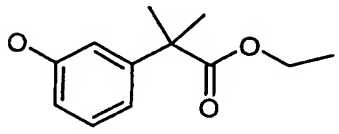
(3-Chloro-4-mercapto-phenyl)-acetic acid methyl ester



This compounds is made from the corresponding phenol analog based on the method outlined in preparation 9.

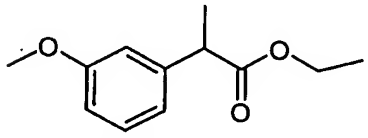
Preparation 22

2-(3-Hydroxy-phenyl)-2-methyl-propionic acid ethyl ester



Step A

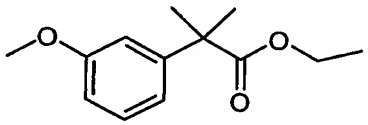
2-(3-Methoxy-phenyl)-propionic acid ethyl ester



To a solution of LDA (2M, 16.5 mL) in THF (10 mL) at - 70 0C is added a solution of (3-methoxy-phenyl)-acetic acid methyl ester (5.4 g, 30 mmol) in THF (10 mL). After 40 minutes at -70 0C, iodomethane (2.5 mL, 40 mmol) is added. The mixture is stirred at room temperature overnight. It is diluted with EtOAc, washed with 1N HCl. The organic layer is dried over Na2SO4 and concentrated to give the titled compound as an oil: 5.9 g (quant.)

Step B

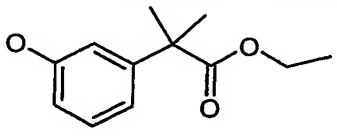
2-(3-Methoxy-phenyl)-2-methyl-propionic acid ethyl ester



To a solution of LDA (2M, 11.4 mL) in THF (10 mL) at - 70 0C is added a solution of 2-(3-methoxy-phenyl)-propionic acid ethyl ester (4g, 20.6 mmol)in THF (10 mL). After 1 hour at -70 0C, iodomethane (1.7 mL, 26.8 mmol) is added and the mixture is stirred at room temperature overnight. It is diluted with EtOAc and washed with 1N HCl. The organic is concentrated to give the titled compound as an oil: 4 g (93%).

Step C

2-(3-Hydroxy-phenyl)-2-methyl-propionic acid ethyl ester

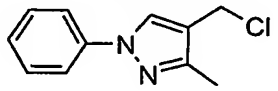


To a solution of 2-(3-Methoxy-phenyl)-2-methyl-propionic acid ethyl ester (4 g, 19.2 mmol) in dichloromethane (20 mL)

at 0 0C is added BBr3 (1M in dichloromethane, 50 mL). After 2 hours at ambient temperature, it is quenched with MeOH. Solvent is evaporated and the residue is partitioned between EtOAc and 1N HCl. The organic is concentrated and purified by column chromatography (0 to 30% EtOAc in hexanes) to give the titled compound as a solid: 2.6 g (70%).
ESMS-: 193 (M-1); 1H NMR is consistent with desired product.

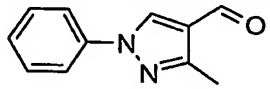
Preparation 23

4-Chloromethyl-3-methyl-1-phenyl-1H-pyrazole



Step A

3-Methyl-1-phenyl-1H-pyrazole-4-carbaldehyde



Phosphoryl chloride (2.62 g, 17.1 mmol) is added dropwise to a solution of 3-methyl-1-phenyl-1H-pyrazole (2.7 g, 17.1 mmol) in DMF (1.25 g, 17.1 mmol) at 100 °C. After heated 3hrs, the reaction mixture is cooled with ice bath and quenched by water. The resulting mixture is basified by 5N NaOH to pH = 4, extracted with ethyl acetate, dried, concentrated. Column chromatography on silica gel yields the title compound.

Step B

(3-Methyl-1-phenyl-1H-pyrazol-4-yl)-methanol

To a solution of 3-Methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (0.9 g, 4.84 mmol) in ethanol (20 mL) is added sodium borohydride (0.18 g, 4.84 mmol) at 0~5 °C, warmed to room temperature. After stirred for 2hrs, quenched by water, ethanol is evaporated. The resiude is diluted with water and extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the title compound.

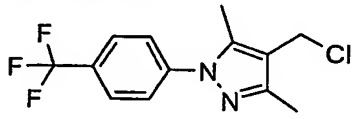
Step C

4-Chloromethyl-3-methyl-1-phenyl-1H-pyrazole

A solution of (3-methyl-1-phenyl-1H-pyrazol-4-yl)-methanol (0.7 g, 3.72 mmol) and triethyl amine (1.04 mL, 7.4 mmol) in methylene chloride (16 mL) is cooled to 0 °C, then MeSO2Cl (0.46 mL, 5.95 mmol) is added dropwise. After 4 hrs, the reaction mixture is diluted with methylene chloride and washed with sodium bicarbonate, water and brine, dried over sodium sulfate. Concentration yields the crude title compound, which is used for the next step without further purification.

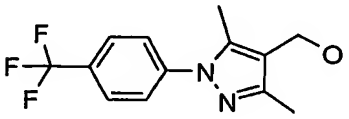
Preparation 24

4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole



Step A

[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



A THF (5 mL) solution of 3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carboxylic acid ethyl ester (1.0 g, 3.2 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (3.2 mL, 3.2 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 0.86 g of the title compound.

Step B

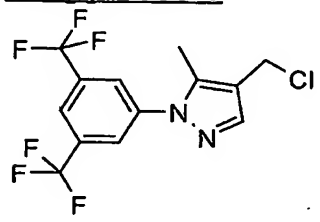
4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A solution of [3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (0.86 g, 3.2 mmol) and triethyl amine 0.9 mL, 6.4 mmol) in methylene chloride (16 mL) is cooled to 0 °C, then MeSO2Cl (0.4 mL) is added dropwise. After 2 hrs, TLC indicated that the reaction is not complete, 10 mol % more of triethyl amine and $MeSO_2Cl$ are added. After additional 2hrs, the reaction mixture is diluted with methylene chloride and washed with sodium bicarbonate, water and brine, dried over sodium sulfate. Concentration yields the crude title compound, which is used for the next step without further purification.

The following compounds are made in a similar manner:

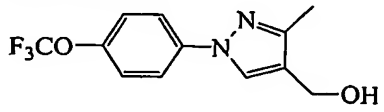
Preparation 25

1-(3,5-Bis-trifluoromethyl-phenyl)-4-chloromethyl-5-methyl-1H-pyrazole



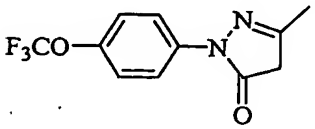
Preparation 26

[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol



Step A

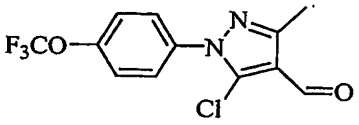
5-Methyl-2-(4-trifluoromethoxy-phenyl)-2,4-dihydro-pyrazol-3-one



To a solution of the trifluoromethoxyphenyl hydrazine HCl salt (10.36g, 45.3 mmol) and toluene (250.0mL) at room temperature is added sodium hydroxide (1.04 g). After stirred overnight, the mixture is treated with ethyl acetoacetate (48.09mL, 0.38m). Reaction mixture is then stirred at room temperature for 66 hrs, diluted with ethyl acetate, washed with water, dried over sodium sulfate. Concentration and column chromatography on silica gel yields the title compound (9.3 g).

Step B

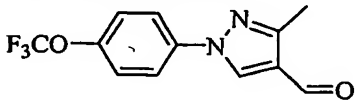
5-Chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde



To DMF (5.03 mL) at 10°C is added $POCl_3$ (6.1 mL) over a period of 30 minutes, to this solid is then added 5-Methyl-2-(4-trifluoromethoxy-phenyl)-2,4-dihydro-pyrazol-3-one (9.3 g, 32.4 mmol), followed by 5.03 mL of DMF. The reaction mixture is slowly heated to 100°C, an additional $POCl_3$ (6.1 mL) is added after 18 hrs. Heating is continued for another 6hrs before the reaction mixture is very carefully reversed quenched into crushed ice, extracted with CH_2Cl_2, washed with 2N NaOH and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes/ethyl acetate yields the title compound (9.6 g).

Step C

3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde

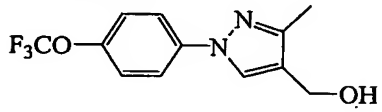


To 5-chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (5.7 g, 17 mmol) dissolved in EtOH (188 mL) is added Et_3N (4.8 mL) and Lindlar catalyst (0.476

g). The mixture is then hydrogenated at room temperature (50psi). After 2.5 hrs, reaction mixture is the filtered through celite, concentrated to a solid. Column chromatography n silica gel eluted with hexanes/ethyl acetate yields the title compound (3.4 g, 66.5 % yiel, and [3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol (0.85 g, 16.5 % yield).

Step D

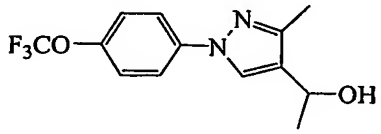
[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol



To a solution of 3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (0.76 g, 2.55 mmol) in ethanol (10 mL) is added NaBH4 (0.1 g, 2.64 mmol). After 2hrs, the reaction is quenched by water, ethanol is evaporated and the residue is extracted with ethyl acetate, dried. Concentration yields the title compound (0.75 g).

Preparation 27

1-[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethanol

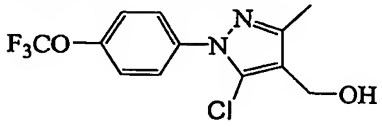


To a solution of 3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (3.4 g, 11.4 mmol) tetrahydrofuran (80 mL) is added methyl magnesium bromide (4.6 mL, 13.7 mmol, 3 M in ether) dropwise at 0°C, the resulting mixture is allowed to stir at room temperature 30 min. The reaction mixture is quenched by aqueous ammonium chloride (30 mL), extracted with ethyl acetate, the combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica gel eluted

with hexanes/ethyl acetate yields the title compound (3.3 g).

Preparation 28

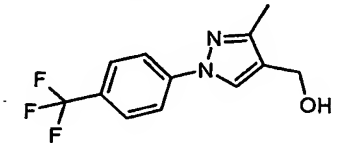
[5-Chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol



To a solution of 5-chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (1.0 g, 3.0 mmol) in ethanol (10 mL) is added NaBH4 (0.113 g, 3 mmol). After 2hrs, the reaction is quenched by water, ethanol is evaporated and the residue is extracted with ethyl acetate, dried. Concentration yields the title compound (0.95 g).

Preparation 29

[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



Step A

The intermediate obtained from Step A is obtained from two separate methods.

Method 1

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

To a solution of 4-(trifluoromethyl)phenylboronic acid (5.04g, 26.5mmol), 3-methylpyrazole (1.1ml, 13.2mmol), and pyridine (2.1ml, 26.5mmol) in dichloromethane (160ml) is added copper(II) acetate (3.61g, 19.9mmol) and 4A molecular sieves (10.0g). The suspension is stirred at ambient temperature in the open air for 48 hours, then filtered through Celite and concentrated in vacuo to a crude solid. Purification by silica flash chromatography (40:1

hexanes:ethyl acetate to 10:1 hexanes:ethyl acetate) yields the title compound as a white solid. MS: m/z (M+1) 227

Method 2

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A mixture of 4-iodobenzotrifluoride (246g, 0.904mol), 3-methylpyrazole (90g, 1.09mol) and potassium carbonate (254g, 1.83mol) in 1,4-dioxane (1L) under N_2 is treated with cupric iodide (1.75g, 9.1mmol) and trans-1,2-cyclohexanediamine (7.5ml, 62.4mmol) and heated at 110°C for 30 hours. The mixture is cooled and diluted with water (1.5L) and ethyl acetate (1.5L). The organic layer is washed with water (1L) and concentrated to an oil. Purification by silica flash chromatography (4:1 hexanes:ethyl acetate) yields the title compound as a white solid. MS: m/z (M+1) 227

Step B

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde

This compound can be prepared by the following two different method:

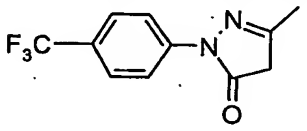
Method I

To a solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (1.88g, 8.31mmol) in DMF (8.0ml) heated at 90° C is carefully added phosphorous oxychloride (1.0ml, 10.8mmol) and the resulting mixture heated at 90° C for 7 hours. Additional phosphorous oxychloride (0.75ml, 8.0mmol) is added and the mixture heated for an additional 2 hours. The mixture is cooled at 0° C, then carefully treated with cold water (75ml). After dilution with diethyl ether (40ml) to dissolve solids, the mixture is adjusted to pH 3 with 5N NaOH. The aqueous layer is extracted with diethyl ether (2 x 25ml), the organic extracts then combined and washed with water, brine, dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (20:1

hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) provided the title compound as a white solid. MS: m/z (M+1) 255.

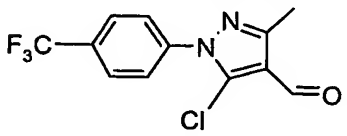
Method II

Step A of method II



To a solution of the Trifluoromethylphenyl Hydrazine (60.4g, 0.34moles) and toluene (250.0mL) at room temperature is added ethylacetoacetate (48.09mL, 0.38m). Reaction solution is then stirred overnight at r.t. for 12 hrs (N.B. reaction generally becomes hazy after an hour of stirring). Heated at reflux with continuous azeotropic removal of water and volatile organic solvents for another 12hrs (note: the volume of toluene removed during azeotrope should be replaced during the course of the reaction). Reaction is monitored by TLC (1:1 EtoAc/Heptane). After the reaction is deemed to be complete, heptane (500.0mL) is added to the hot solution. An off tan precipitate is observed upon equilibration to ambient temperature. The tan precipitate is filtered and the cake washed with heptane (75.0mL), dried in an oven at 50°C overnight (mass = 75.39g; 90% wt. Yield; ^1H ($CDCl_3$+ $DMSOd_6$) δ 1.82 (s, 3H), 3.16 (s, 2H), 7.22-7.25 (d, 2H, J = 8.8Hz), 7.57-7.59 (d, 1H, J = 8.8Hz), 7.66-7.68 (d, 1H, J = 8.5Hz).

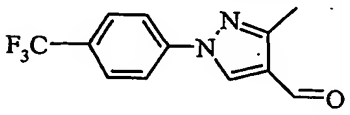
Step B of method II



To DMF (44.56mL, 0.57m) at 10°C is added $POCl_3$ (52.68mL, 0.57m) over a period of 30 minutes (caution solution solidifies after addition). To this solid is then added the pyrazolone (70.0g, 0.28m). Slowly heated mixture until dissolution is observed at 75-80°C (To aid the dissolution,

an extra 40mL of DMF is added). The dark reaction solution is then heated at 90-100°C for 18hrs, after which an additional $POCl_3$ (52.6mL) is added (reaction is monitored by TLC 1:1 EtoAc/Heptane). Heating is continued for another 6hrs before the reaction mixture is very carefully reversed quenched into crushed ice over a period of 2hrs. (Extreme caution: quenching is quite exothermic and should be done very carefully. Possible induction period can be observed during quenching of excess $POCl_3$). A dark brown precipitate is observed after quenching. On equilibration to r.t., the precipitate is extracted with CH_2Cl_2 (500.0mL), washed with 2N NaOH (2X500ml), treated with Darco and anh. $MgSO_4$. Subsequent filtration over hyflo and concentration at reduced pressure on the rotovap afforded a tan precipitate (mass = 72.0g). The purity of the precipitate can be upgraded by dissolving it in a hot EtoAc (200ml), followed by a quick plug over silica gel. Concentration of the filtrate on the rotovap affords a tan solid (mass = 68.4g; 82% wt. Yield; ^1H ($CDCl_3$) δ 2.54 (s, 3H), 7.72-7.81 (m, 4H), 9.99 (s, 1H, CHO).

Step C of method II



To Chloro/formyl starting material (520mg, 1.8mm) dissolved in EtOH (20.0mL) is added Et_3N (0.5mL) and Lindlar catalyst (0.05g). The mixture is then hydrogenated at r.t (50psi). After 2.5 hrs, ^1H nmr of an aliquot after a brief work up indicated product with no observable starting material. Reaction mixture is the filtered over hyflo, concentrated to a solid. To the solid is added CH_2Cl_2 (40.0mL) and 1NHCl (20.0mL) with stirring. Subsequent separation of lower organic layer, drying and concentrating on the rotovap afforded a tan precipitate (mass = 455mg; 100% wt.yield; ^1H ($CDCl_3$) δ 2.57 (s, 3H), 7.71-7.74 (d, 2H, J = 8.4Hz), 7.82-7.85 (d, 2H, J = 8.5Hz), 8.43 (s, 1H), 10.00 (s, 1H, CHO).

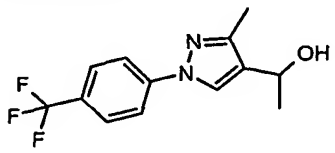
Step C

[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol

To a chilled (0°C) suspension of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (350mg, 1.37mmol) in ethanol (6 ml) is added sodium borohydride (52mg, 1.37mmol) portionwise over two minutes. The reaction mixture is removed from the cold bath and stirred for one hour. After quenching with water (25ml), the reaction mixture is extracted with diethyl ether (3 x 15ml). The combined organic extracts are washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 257.

Preparation 30

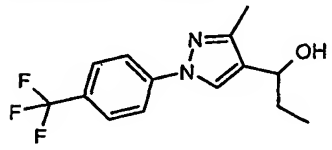
1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol



To a cooled (0°C) solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (500mg, 1.96mmol) in tetrahydrofuran (2.5ml) is added a solution of methyl magnesium bromide (3M in diethyl ether)(0.98ml, 2.94mmol) over 4 minutes. The mixture is removed from the cold bath and stirred for two hours, then cooled again to 0°C and treated with saturated aqueous ammonium chloride (30ml) followed by water (20ml). After extraction with ethyl acetate (3 x 20ml), the combined organic extracts are washed with brine, then dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (20:1 hexanes:ethyl acetate to 3:1 hexanes:ethyl acetate) provided the title compound as a racemic white solid.
MS: m/z (M+1) 271.

Preparation 31

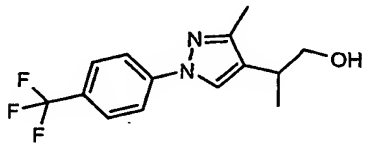
1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



To a cooled (0°C) solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (300mg, 1.18mmol) in tetrahydrofuran (3.0ml) is added a solution of ethyl magnesium bromide (3M in diethyl ether) (0.59ml, 1.77mmol) over 2 minutes. The mixture is removed from the cold bath and stirred for 3 hours, then cooled again to 0°C and treated with saturated aqueous ammonium chloride and water. After extraction with ethyl acetate (3 x 15ml), the combined organic extracts are washed with brine, then dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (25:1 hexanes:ethyl acetate to 4:1 hexanes:ethyl acetate) provided the title compound as a racemic white solid. MS: m/z (M+1): 285.

Preparation 32

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



Step A

1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone

To a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol (2.95g, 10.9mmol) in chloroform (80ml) is added activated manganese(IV)dioxide (9.5g, 109mmol), and the resulting suspension heated at reflux for 36 hours. The mixture is cooled and filtered through Celite,

washed with chloroform, and the filtrate concentrated to a crude solid. Purification by silica flash chromatography (20:1 hexanes:ethyl acetate to 2:1 hexanes:ethyl acetate) provided the title compound as a white solid. MS: m/z (M+1) 269.

Step B

4-(2-Methoxy-1-methyl-vinyl)-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A solution of potassium tert-butoxide (3.74g, 33.3mmol) in tetrahydrofuran (25ml) is added dropwise over 15 minutes to a cooled (0°C) suspension of methoxymethyltriphenylphosphonium chloride (11.41g, 33.3mmol) in tetrahydrofuran (35ml) . The mixture is stirred at 0°C for 20 minutes and then treated dropwise over 5 minutes with a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (3.0g, 11.1mmol) in tetrahydrofuran (20ml). After addition is complete, the mixture is removed from the cold bath and stirred for 2 hours, then diluted with brine (300ml) and diethyl ether (150ml). The organic layer is removed, and the remaining aqueous layer extracted with diethyl ether (2 x 25ml). The organic extracts are combined, washed with brine, dried (Na_2SO_4), and concentrated to an oil which is purified by silica flash chromatography (30:1 hexanes:ethyl acetate to 8:1 hexanes:ethyl acetate) to provide the title compound as an oil. MS: m/z (M+1) 297.

Step C

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde

A cooled (0°C) solution of 4-(2-Methoxy-1-methyl-vinyl)-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (2.7g, 9.11mmol) in tetrahydrofuran (25ml) is treated dropwise over 5 minutes with concentrated hydrochloric acid (15ml) and the mixture stirred at 0°C for 3 hours. After dilution with

diethyl ether (50ml), the reaction mixture is adjusted to pH 7 with 1N NaOH. The aqueous layer is extracted with diethyl ether (2 x 30ml), the organic extracts then combined and washed with brine and dried (Na_2SO_4). Concentration provided the title compound as an oil which slowly crystallized and is used without further purification. MS: m/z (M+1) 283.

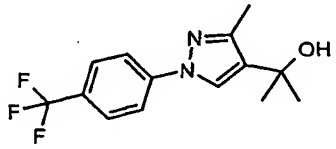
Step D

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol

Sodium borohydride (132mg, 3.5mol) is added in one portion to a cooled (0°C) solution of 2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde (2.0g, 7.08mmol) in ethanol (30ml), and the mixture stirred at 0°C for 1 hour. After quenching with water (55ml), the reaction mixture is extracted with diethyl ether (3 x 25ml). The combined organic extracts are washed with water, brine, then dried (Na_2SO_4) and concentrated to a solid which is purified by silica flash chromatography (20:1 hexanes:ethyl acetate to 3:1 hexanes:ethyl acetate) to provide the title compound as a racemic solid. MS: m/z (M+1) 285.

Preparation 33

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-2-ol

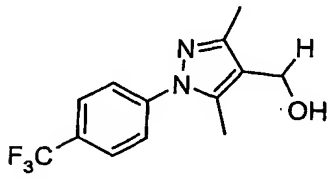


To a cooled (0°C) solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (1.0g, 3.72mmol) in tetrahydrofuran (10ml) is added methylmagnesium bromide (3M in diethyl ether)(1.9ml, 5.6mmol) dropwise over 3 minutes. After stirring at 0°C for 90 minutes, the mixture is adjusted to pH 6 with 1N HCl, and then diluted with diethyl ether (30ml) and water (40ml). The organic layer is

removed and the remaining aqueous layer extracted with diethyl ether (2 x 25ml). The combined organic extracts are combined and washed with water, brine, dried (Na_2SO_4), and concentrated to an oil. Purification by silica chromatography (20:1 hexanes:ethyl acetate to 4:1 hexanes:ethyl acetate) provided the title compound as an oil. MS: m/z (M+1) 285.

Preparation 34

[3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazol-4-yl]-methanol



Step A

3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazole

To a solution of 4-(trifluoromethyl)-phenylhydrazine (10 g, 56.77 mmol) in ethanol (150 mL), add 2,4-pentanedione (5.83 mL, 56.77 mmol) and a catalytic amount of *p*-toluenesulfonic acid. Heat the resulting mixture to reflux for 5 h. Then, allow the reaction mixture to cool to room temperature. Concentrate on rota-vapor. Partition the residue between EtOAc (150 mL) and H_2O (100 mL). Wash the organic extract with brine (100 mL), dry over Na_2SO_4, filter and concentrate to afford title compound as an orange oil (quantitative yield) that is used directly for the next step. MPLC ($M^+ + 1 = 241.1$).

Step B

3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazole-4-carbaldehyde

To a solution of 3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1*H*-pyrazole (10.31 g, 42.92 mmol)) in DMF (42 mL) add $POCl_3$

(5.2 mL, 55.77 mmol). Stir the resulting mixture at 90°C for 12 h, and then add $POCl_3$ (3.84 mL, 41.2 mmol) and stir again at 90°C for additional 6 hours. Monitor the starting material consumption by TLC. When reaction is completed, then allow to cool to room temperature. Partition the residue between H_2O (100 mL) and Et_2O (3 x 100 mL), and extract again the aqueous layer with CH_2Cl_2 (3x 100 mL). Wash each organic extract separately with brine (2 x 100 mL), and dry over Na_2SO_4. Filter the solutions and concentrate together to afford the crude product. Purificate by silica gel column chromatography (0% to 25% EtOAc/hexanes) to obtain (7.04 g, 61%). ^1H NMR ($CDCl_3$): δ 10.05 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 2.61 (s, 3 H), 2.53 (s, 3 H).

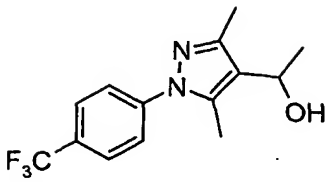
Step C

[3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazol-4-yl]-methanol

3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazole-4-carbaldehyde (2.0 g, 7.46 mmol) is taken into EtOH (60 mL) at 0°C (ice bath). Add sodium borohydride (0.141 g, 3.73 mmol), in one portion and let the mixture warm to room temperature while stirring for 12 h. Quench with H_2O (80 mL), extract with EtOAc (3 x 50 mL). Wash the combined organic extracts with brine (3 x 30 mL), dry over $NaSO_4$, filter and concentrate. Silica gel column chromatography yields the title compound as a white solid (1.97 g, 98%). MPLC ($M^+ + 1 = 271.1$). ^1H NMR ($CDCl_3$): δ 7.73 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 4.58 (s, 2 H), 2.39 (s, 3 H), 2.36 (s, 3 H).

Preparation 35

1-[3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazol-4-yl]-ethanol



Prepare a solution of 3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazole-4-carbaldehyde (7.04 g, 26.26 mmol) in THF (50 mL) and cool it to 0°C using an ice bath. A solution of methyl magnesium bromide (1.0 M) (40 mL, 39.39 mmol) is added over 5 min. Once the addition is completed, remove the ice bath and stirred for additional 2 hours. Cool again to 0°C and partition between saturated NH_4Cl (80 mL) and EtOAc (150 mL). Wash the organic extract with H_2O (2 x 50 mL), then with brine (3 x 50 mL), and dry over Na_2SO_4, filter and concentrate. Purify on silica gel column chromatography to afford the title compounds as yellow solids (6.77 g, 91%). MPLC ($M^+ + 1 = 285.1$).

The following compound is made in a similar way.

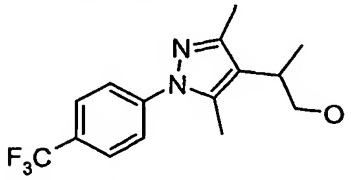
Preparation 36

1-[3,5-dimethyl-1-(4trifluoromethyl-phenyl)-1*H*-pyrazol-4-yl]-propanol

^1H NMR ($CDCl_3$: δ 7.71 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 4.66 (t, *J* = 7.3 Hz, 1 H), 2.37 (s, 3 H), 2.35 (s, 3 H), 2.04-1.91 (m, 1 H), 1.85-1.78 (M, 1 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

Preparation 37

2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



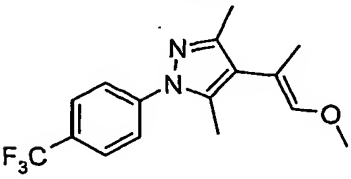
Step A

1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone

Dissolve 1-[3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1*H*-pyrazole-4-yl]-ethanol (5.09 g, 17.905 mmol) in $CHCl_3$ (80 mL) and to this solution, add activated manganese (IV) dioxide (15.57 g, 179.05 mmol). Heat to reflux the resulting suspension for 36 hours. After that time, allow to cool to room temperature, then filter through a short pad of Celite. Concentrate the filtrate to afford the title compound as an off-white solid, and use without further purification in next Reaction E. (4.87 g, 96%). MPLC ($M^+ + 1 = 283.1$).

Step B

4-(2-methoxy-1-methyl-vinyl)-1*H*-pyrazol



Suspend methoxymethyl triphenylphosphonium chloride (17.75 g, 51.79 mmol) in THF (40 mL) at room temperature and then cool to 0°C (ice bath). Suspend potassium tert-butoxide (5.81 g, 51.79 mmol) in THF (30 mL). Add the potassium tert-butoxide suspension onto the methoxymethyl triphenylphosphonium chloride suspension in a dropwise fashion. Stir for 20 minutes. Then add dropwise a solution of 1-[3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1*H*-pyrazole-4-yl]-ethanone (4.87 g, 17.26 mmol) in THF (80 mL) along 5 minutes. After completion of the addition, remove the

cooling bath. Stir for 2 additional hours. Partition the reaction mixture between EtOAc (250 mL) and H_2O (100 mL). Wash the organic extract with brine (3 x 150 mL), dry over Na_2SO_4, filter and concentrate to afford the crude product. Purification using silica gel column chromatography (0% to 15% EtOAc/hexanes) gave the title compound as an off-white solid. (5.30 g, 99%). ^1H NMR ($CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2 H), 7.60 (d, J = 8.7 Hz, 2 H), 6.1 (s, 1 H), 3.62 (s, 3 H), 2.60 (s, 3 H), 1.83 (s, 3 H).

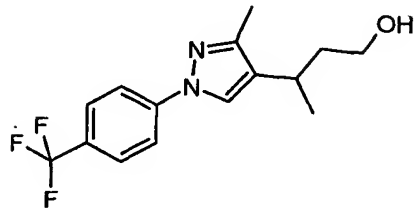
Step C

2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol

Dissolve 4-(2-methoxy-1-methyl-vinyl)-1*H*-pyrazol (6.06 g, 19.52 mmol) in acetonitrile (200 mL) at room temperature. Add sodium iodide (2.93 g, 19.52 mmol) and stir the reaction mixture for 3 minutes. Cool while stirring to 0°C (ice bath). Add trimethylsilylchloride (2.5 mL, 19.52 mmol) dropwise. Remove the ice bath and stir at room temperature for 2 hours. Monitor the consumption of the starting material by TLC. When the reaction is completed, add 5% sodium sulfate solution (100 mL) and EtOAc (250 mL). Extraction with EtOAc and wash the combined organic solutions with brine (100 mLx3). Dry over Na_2SO_4, and concentrate to obtain a yellow solid. This solid is taken up in 150 mL of EtOH and stirred at room temperature. Cool the mixture to 0°C (ice bath) and add sodium borohydride (390 mg., 20.6 equivalents) in one portion. Remove the cooling bath after addition and stir the reaction mixture for 4 hours at room temperature. Monitor the reaction by TLC. Dilute with EtOAc, extract with 200 mL of EtOAc wash the combined organic phases with brine, (3x50 mL), dry over Na_2SO_4, and concentrate to obtain the title compound as a off-white solid. Purify by silica gel column chromatography with 30% EtOAc in Hexanes. (3.82 g, 62%).MPLC ($M^+ + 1$ = 299.1).

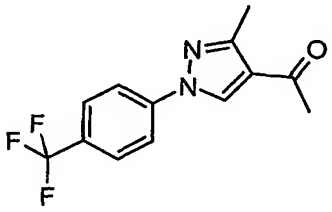
Preparation 38

3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butan-1-ol



Step A

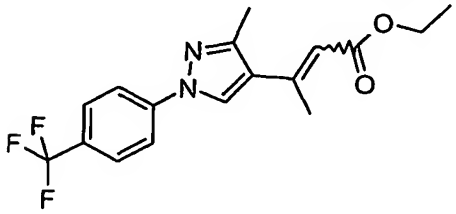
1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone



To an ambient temperature solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol (5.0 g, 18.50 mmol) in CH2Cl2 (100 ml) is added manganese (IV) dioxide (12.0 g, 138 mmol) and heated to reflux overnight. TLC (100% EtOAc) indicates complete consumption of starting material. The reaction mixture is fltered through a bed of silica gel resting on ceelite. The filtrate is concentrated and recrystallized from hot ethyl acetate/hexanes yields the title compound (4.93 g, 99%).

Step B

3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-but-2-enoic acid ethyl ester

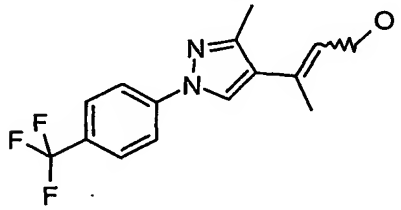


To a 0 C suspension of sodium hydride (7.2 g, 180 mmol, 60% oil dispersion) in THF (50 ml) prewashed with hexanes (100 ml) is added a solution of triethyl phosphonoacetate (32.5

ml, 163.7 mmol) in THF (50 ml). The reaction mixture is warmed to room temperature for 1h and cooled back to 0 C. At which point a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (4.93 g, 16.37 mmol) in THF (100 ml) is added and the reaction mixture heated to reflux for 6h. TLC (20% EtOAc/hexane) indicates complete consumption of starting material. Reaction is cooled to room temperature and quenched with saturated aqueous NH_4Cl. The reaction mixture is concentrated and the aqueous layer extracted with EtOAC (3 x 200 ml). The combined organic layers are washed with brine (100 ml), dried ($MgSO_4$), filtered, concentrated and chromatographed (120 g SiO_2, 10% EtOAc/Hexanes) to yield the title compound (5.41 g, 96%).

Step C

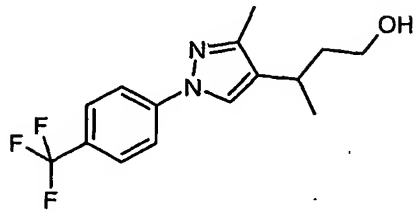
3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-but-2-en-1-ol



To a 0 C solution of 3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-but-2-enoic acid ethyl ester (5.41 g, 15.99 mmol) in THF (200 ml) is added portion-wise lithium aluminum hydride (1.82 g, 47.97 mmol) and heated to reflux. After 1h TLC (20% EtOAc/hexane) indicates complete consumption of starting material. The reaction is cooled to 0 C and quenched by the slow addition of water, 5N NaOH and water. The suspension, which is formed, is diluted with EtOAc (200 ml) and filtered. The filtrate is concentrated and chromatographed (120 g SiO_2, 20% EtOAc/Hexanes) to yield (4.37 g, 86%)a 4:1 mixture of title compound and the saturated alkane.

Step D

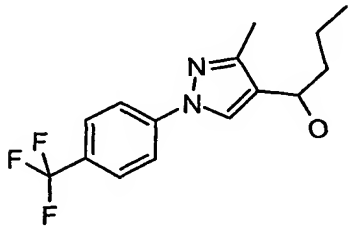
3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butan-1-ol



To an ambient temperature suspension of palladium on carbon (1.5 g, 10% wt) in a solution of 3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-but-2-en-1-ol (4.3 g, 14.51 mmol) in ethanol (30 ml) is added an atmosphere of hydrogen gas and continues to stir at room temperature. After 5h LC/MS indiacated complete conversion of SM to desired product. Reaction mixture is filtered through ceelite and concentrated to yield the title compound (3.92 g, 91%).

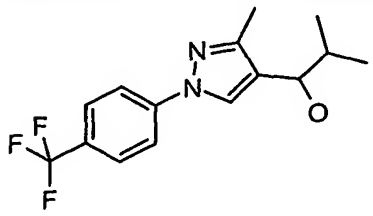
Preparation 39

1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butan-1-ol



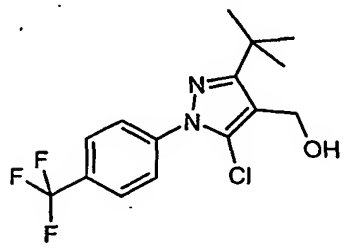
Preparation 40

2-Methyl-1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



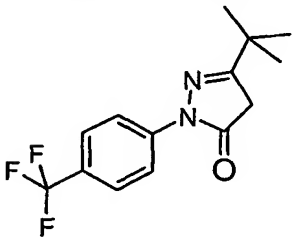
Preparation 41

[3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



Step A

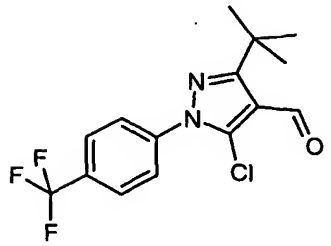
5-tert-Butyl-2-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazol-3-one



To an ambient temperature solution of Trifluoromethylphenyl hydrazine (9.0 g, 51.1 mmol) is added 4,4-Dimethyl-3-oxo-pentanoic acid ethyl ester (9.13 ml, 57.1 mmol) and stirred overnight. The reaction mixture is then refluxed with continuous azeotropic removal of water and volatile organics for anther 6 hours. TLC (30% EtOAc/hexane) indicates complete consumption of starting material. Heptane is added to the hot solution. As the solution cools a tan solid precipitates and is filtered. The filter cake is washed with heptane and dried to yield the title compound (14.50 g, 99%).

Step B

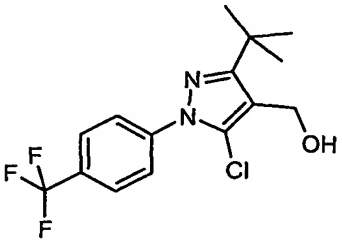
3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde



To a 10 C solution of phosphorous oxychloride (9.35 ml, 102.2 mmol) in DMF (30 ml) is added solid 5-tert-Butyl-2-(4-trifluoromethyl-phenyl)-2,4-dihydro-pyrazol-3-one (14.5 g, 51.1 mmol) and the reaction mixture is heated to 100 C overnight. TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction is quenched by pouring into ice (1L). Once warmed to room temperature the mixture is extracted with CH_2Cl_2 (3 x 300 ml). The combined organic layers are washed with 2N NaOH and water, dried ($MgSO_4$), filtered, concentrated and chromatographed (330 g SiO_2, 10% EtOAc/Hexanes) to yield the title compound (14.7 g, 87%).

Step C

[3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol

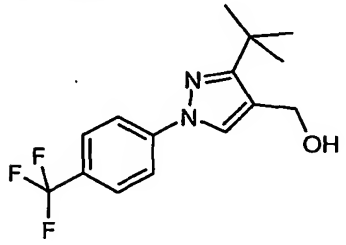


To a 0 C solution of 3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (2.0 g, 6.05 mmol) in THF/MeOH (60/15 ml) is added portion-wise sodium borohydride (458 mg, 12.1 mmol) and warmed to room temperature. After 1h TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction mixture is concentrated and the residue is partitioned between EtOAc (100 ml) and 0.2N HCl (50 ml). The aqueous layer is extracted with a second portion of EtOAc (50 ml). The combined organic layers are washed with brine, dried

($MgSO_4$), filtered and concentrated to yield the title compound (1.99 g, 99%).

Preparation 42

[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



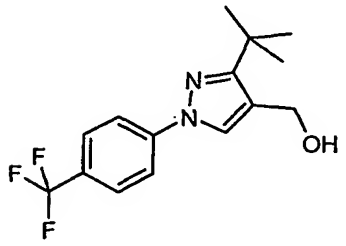
Step A

3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde

To an ambient temperature solution of 3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (9.0 g, 27.21 mmol) in EtOAC/Et_3N (4/9 ml) is added 5% $Pd/CaCO_3$(Pb) (908 mg). The reaction mixture is stirred under 60 psi of hydrogen overnight. Catalyst is filtered and the filtrate is concentrated giving the title compound (5.08 g, 63%).

Step B

[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



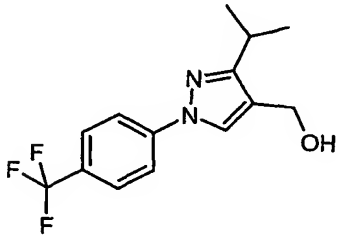
To a 0 C solution of 3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (2.4 g, 8.1 mmol) in THF/MeOH (80/20 ml) is added portion-wise sodium borohydride (460 mg, 12.15 mmol) and warmed to room temperature. After 1h TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction mixture is concentrated and

the residue is partitioned between EtOAc (100 ml) and 0.2N HCl (50 ml). The aqueous layer is extracted with a second portion of EtOAc (50 ml). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound (2.28 g, 94%).

The following compounds were prepared in a similar manner using the appropriate β-keto esters.

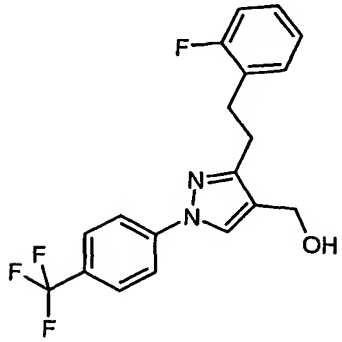
Preparation 43

[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



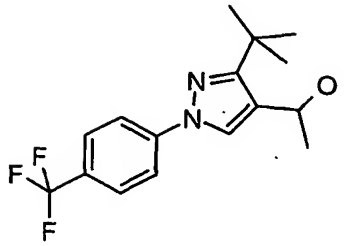
Preparation 44

[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



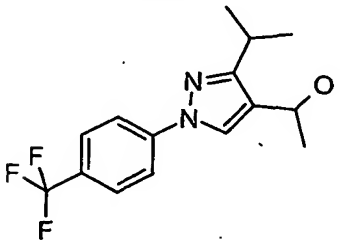
Preparation 45

1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol



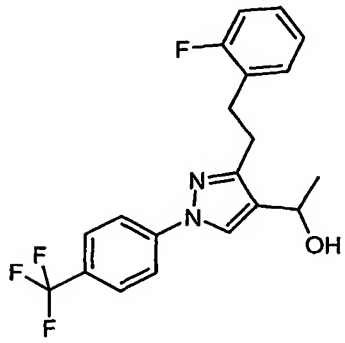
Preparation 46

1-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol



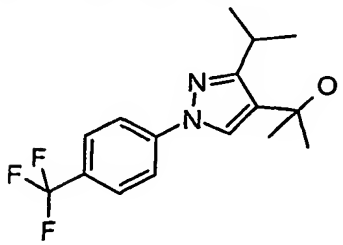
Preparation 47

1-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol



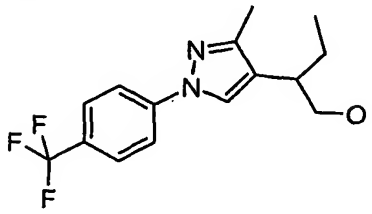
Preparation 48

2-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-2-ol



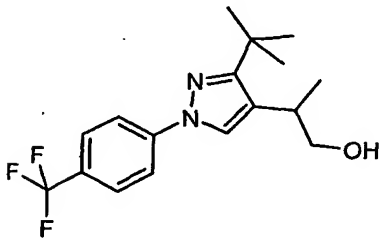
Preparation 49

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butan-1-ol



Preparation 50

2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



To a -78 C solution of 3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (5.0 g, 16.87 mmol) in THF (170 ml) is added methylmagnesium bromide (24.1 ml, 33.75 mmol, 1.4 M in Et_2O) dropwise and is allowed to warm to room temperature. After 1h TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction is quenched with saturated aqueous NH_4Cl. The reaction mixture is concentrated and the aqueous layer extracted with EtOAC (3 x 250 ml). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound (5.27 g, 100%).

Step B

1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone

To an ambient temperature solution of 1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol (5.27 g, 16.87 mmol) in CH_2Cl_2 (100 ml) is added manganese (IV) dioxide (13.2 g, 152 mmol) and heated to reflux overnight.

TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction mixture is filtered through a bed of silica gel resting on ceelite. The filtrate is concentrated and recrystallized from hot ethyl acetate/hexanes to yield the title compound (4.89 g, 93%).

Step C

3-tert-Butyl-4-(2-methoxy-1-methyl-vinyl)-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

To a an ambient temperature suspension of potassium tert-butoxide (4.01 g, 35.77 mmol) in THF (100 ml) is added (Methoxymethyl)triphenylphosphonium chloride (12.26 g, 35.57 mmol) and is stirred at room temperature for 30 min. 1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (3.7 g, 11.92 mmol) is added and the reaction mixture continues to stir at room temperature. After 2h TLC (30% EtOAc/hexane) indicates complete consumption of starting material. Reaction is quenched with saturated aqueous NH_4Cl. The reaction mixture is concentrated and the aqueous layer extracted with EtOAc (3 x 200 ml). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, concentrated and chromatographed (120 g SiO_2, 10% EtOAc/Hexanes) to yield the title compound (2.87 g, 71%).

Step D

2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde

To a 0 C solution of 3-tert-Butyl-4-(2-methoxy-1-methyl-vinyl)-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (2.66 g, 7.86 mmol) in THF (20 ml) is added dropwise concentrated hydrochloric acid (12.5 ml) and the reaction is warmed to room temperature. After 1h TLC (30% EtOAc/hexane) indicates complete consumption of starting material. The reaction mixture is diluted with water and the pH is adjusted to 8 with solid $NaHCO_3$. The reaction mixture is concentrated and the aqueous layer extracted with EtOAC (3 x 100 ml). The combined organic layers are washed with brine, dried

($MgSO_4$), filtered, concentrated and chromatographed (120 g SiO_2, 10% EtOAc/Hexanes) to yield the title compound (2.42 g, 95%).

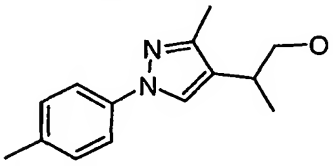
Step E

2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol

To a 0 C solution of 2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde (2.55 g, 7.86 mmol) in THF/MeOH (80/20 ml) is added portion-wise sodium borohydride (595 mg, 15.72 mmol) and warmed to room temperature. After 1h TLC showed no SM. The reaction mixture is concentrated and the residue is partitioned between EtOAc (100 ml) and 0.2N HCl (50 ml). The aqueous layer is extracted with a second portion of EtOAc (50 ml). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound (2.50 g, 98%).

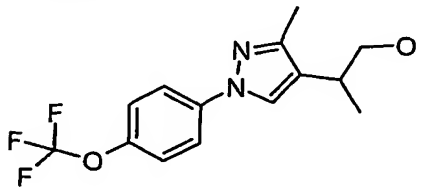
Preparation 51

2-(3-Methyl-1-p-tolyl-1H-pyrazol-4-yl)-propan-1-ol



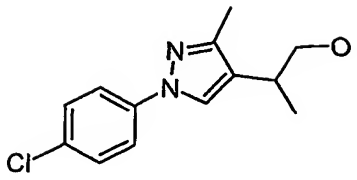
Preparation 52

2-[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



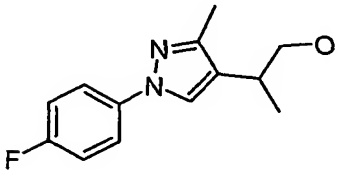
Preparation 53

2-[1-(4-Chloro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propan-1-ol



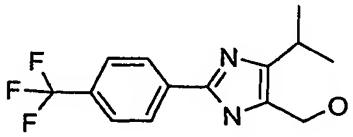
Preparation 54

2-[1-(4-Fluoro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propan-1-ol



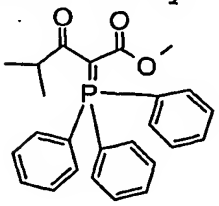
Preparation 55

[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



Step A

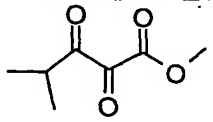
4-Methyl-3-oxo-2-(triphenyl-15-phosphanylidene)-pentanoic acid methyl ester



To a solution of isobutric acid (4.4 g, 50 mmol) and (triphenyl-15-phosphanylidene)-acetic acid methyl ester (16.7 g, 50 mmol)in methylene chloride (500 mL) is added DMAP (610 mg, 5 mmol) and EDCI (9.6 g, 50 mmol) at 0~5 °C, then warmed to room temperature. The reaction mixture is quenched by 1N NaOH, layers are separated, the organic layer is washed with water and brine, dried over sodium sulfate. Concentration yields the title compound.

Step B

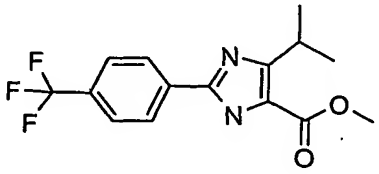
4-Methyl-2,3-dioxo-pentanoic acid methyl ester



To a solution of 4-Methyl-3-oxo-2-(triphenyl-15-phosphanylidene)-pentanoic acid methyl ester (2.0 g, 4.95 mmol) in methylene chloride is bubbled ozone for 30 min at -78 °C, then the reaction mixture is loaded on silica gel column, eluted with hexanes and ethyl acetate giving 0.51 g of the title compound.

Step C

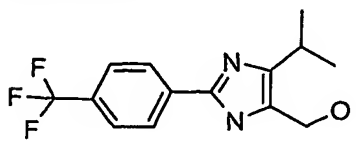
5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester



To a slurry of NH4OAc (2.48 g) in acetic acid is added 4-Methyl-2,3-dioxo-pentanoic acid methyl ester (0.51 g, 3.22 mmol) and 4-Trifluoromethyl-benzaldehyde (1.11g). The mixture is heated at 60 oC for 1h, acetic acid is evaporated. The residue is dissolved in ethyl acetate, washed with NaHCO3, water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel yields the title compound (0.5 g).

Step D

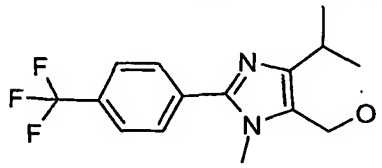
[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



A THF (5 mL) solution of 5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester(0.47 g, 1.51 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (1.51 mL, 1.51 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 0.4 g of the title compound.

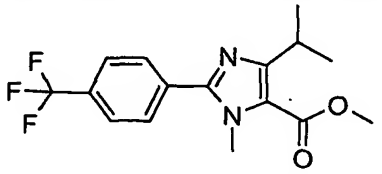
Preparation 56

[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



Step A

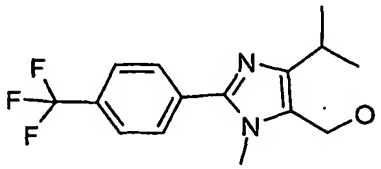
5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester



To a solution of 5-isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester (3.0 g, 9.6 mmol) in DMF (100 mL) is added sodium hydride (60 %, 0.58 g) at 0~5 °C. The mixture is stirred at 0~5 °C for 30 min, methyl iodide (1.2 mL) is added. The reaction mixture is warmed to room temperature and stirred overnight, wuenched by water, extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the title compound (2.5 g).

Step B

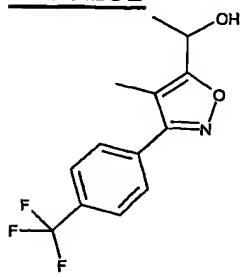
[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



THF (10 mL) solution of 5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester(2.36 g, 7.23 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (7.5 mL, 7.5 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 1.9 g of the title compound.

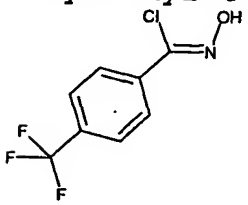
Preparation 57

1-[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol



Step A

N-Hydroxyl-4-trifluoromethyl-benzimidoyl chloride



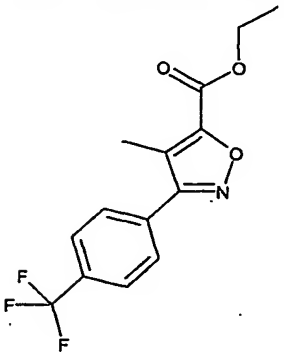
4-Trifluoromethyl-benzaldehyde (3.48 g, 20.0 mmol) in EtOH (50 mL) is added NH_2OH-HCl (1.53 g, 22.0 mmol). The mixture is stirred and heated to reflux at 84 °C for 2 hours. It is then cooled down and concentrated and purified on silica gel

chromatography column with 10-20% EtOAc/Hexanes to obtain the oxime intermediate.

The oxime intermediate (2.40 g, 12.7 mmol) is then dissolved in DMF (10 mL) and added the NCS (0.93 g, 6.95 mmol). Use heat gun to initiate the reaction and then add another portion of NCS (0.93 g, 6.95 mmol). The reaction mixture is stirred at room temperature for 2 hours and quenched with water (50 mL). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 20-50% EtOAc/Hexanes to yield the title compound (2.60 g, 92%).

Step B

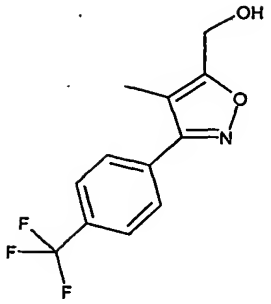
4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazole-5-carboxylic acid ethyl ester



To a solution of N-Hydroxyl-4-trifluoromethyl-benzimidoyl chloride (0.65 g, 2.91 mmol) and but-2-ynoic acid ethyl ester (0.49 g, 4.36 mmol) in EtOAc (3.0 mL) is added Et_3N dropwisely while stirred vigorously. The resulted suspension is heated to 80 °C for 12 hours. It is then filtered and the filtrate is purified on silica gel chromatography column with 10-15% EtOAc/Hexanes to obtain the product (410 mg, 47%).

Step C

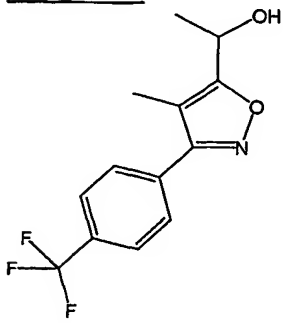
[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-methanol



A solution of 4-methyl-3-(4-trifluoromethyl-phenyl) isoxazole-5-carboxylic acid ethyl ester (810 mg, 2.71 mmol) in THF (30 mL) is treated with $LiBH_4$ (295 mg, 13.5 mmol). The suspension is stirred at room temperature for 48 hours and then quenched water (20 mL). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 50% EtOAc/Hexanes to yield the title compound (480 mg g, 69%).

Step D

1-[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol



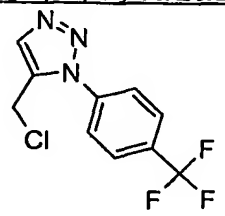
A solution of [4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-methanol (251 mg, 0.976 mmol) is treated with MnO_2 (168 mg, 1.95 mmol) and the suspension is stirred at 75 °C for 24 hours. The mixture is filtered and purified on silica gel chromatography column with 25% EtOAc/Hexanes to yield the aldehyde intermediate (165 mg).

A solution of that aldehyde intermediate (165 mg, 0.647 mmol) in THF (10 mL) at -78 °C is treated with MeMgBr (0.43 mL, 3.0 M). The mixture is stirred while warmed up to room temperature over 60 minutes. The reaction is then quenched

with water (1.0 mL) and HCl (5 mL, 0.1 N). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 30% EtOAc/Hexanes to yield the title compound (160 mg, 91%).

Preparation 58

5-Chloromethyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazole



Step A

To a slurry of (4-Trifluoromethyl-phenyl)-hydrazine (1.8 g, 10.22 mmol) in water (50 mL) at 0°C under nitrogen is slowly added concentrated hydrochloric acid (14 mL). In a separate round bottom flask, sodium nitrite (2.0 g, 34 mmol) is dissolved in water (10 mL) and transferred to the reaction slurry slowly by pipette. The mixture is allowed to stir at 0°C open to air and monitored by TLC. Upon complete consumtion of starting material, the reaction is diluted with ethyl acetate and the two phases are seperated. The organic layer is washed, dried, filtered and concentrated. The crude 1-azido-4-trifluoromethyl-benzene is used immediately without further purification.

Step B

1-azido-4-trifluoromethyl-benzene (10.22 mmol) is dissolved in anhydrous dimethyl formamide (4 mL) and methylpropriolate (3.6 mL, 40 mmol) is added with stirring under nitrogen at room temperature. The reaction is heated to 45°C and monitored by TLC. After the starting material is completely consumed, the reaction is cooled to room temperature and concentrated. The reaction is diluted with chloroform and washed with water and brine, dried over sodium sulfate, then concentrated. The residue is further purified using flash

column chromatography. The regioisomers 3-(4-Trifluoromethyl-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.074g, 0.2731 mmol), 4% yield, and 1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.510g, 1.88 mmol), 18% yield, are formed in roughly a 1:4 ratio.

Step C

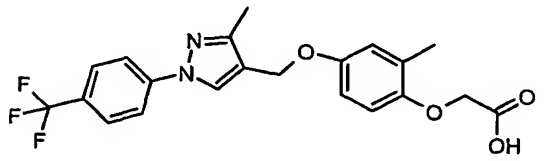
1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.510g, 1.88 mmol) is dissolved into anhydrous tetrahydrofuran (10 mL) and cooled to 0°C under nitrogen. A solution of lithium aluminum hydride, 1.0M in THF, (1.90 mL, 1.90 mmol) is slowly added and the reaction is monitored by TLC. Upon complete consumtion of starting material, the reaction is quenched with water, 20% sodium hydroxide, and water additions, diluted with diethyl ether, followed by filtration through a celite plug. The two phases are seperated. The organic layer is washed, dried, filtered and concentrated. The crude [1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (0.314 g, 1.29 mmol), 69% yield, is used without further purification.

Step D

[1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (0.314 g, 1.29 mmol), is dissolved into anhydrous dichloromethane (5 mL) and cooled to 0°C under nitrogen. Triethyl amine (0.360 mL, 2.58 mmol) and methane sulfonyl chloride (0.150 mL, 1.94 mmol) are then slowly added and the reaction is monitored by TLC. Upon complete consumtion of starting material, the reaction is diluted with dichloromethane and extracted against saturated sodium bicarbonate solution. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate, and concentrated. The crude 4-Chloromethyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazole (0.337 g, 1.29 mmol), 100% yield, is used without further purification.

Example 1

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid



Step A

4-Chloromethyl-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

To a cooled (0°C) solution of [3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (333mg, 1.29mmol) and triethylamine (0.36ml, 2.58mmol) in dichloromethane (5ml) is added methanesulfonyl chloride (0.16ml, 2.06mmol) dropwise over 5 minutes. After stirring at 0°C for 2 hours, the mixture is diluted with dichloromethane (15ml) and washed with saturated aqueous sodium bicarbonate (2 x 15ml). The organic layer is washed with water, brine, dried (Na_2SO_4), and concentrated to the title compound as a solid and is used without further purification. MS: m/z (M+1) 275.

Step B

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid methyl ester

To a solution of (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (99.3mg, 0.50mmol) and 4-Chloromethyl-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (167mg, 0.61mmol) in acetonitrile (1.5ml) is added cesium carbonate (260mg, 0.80mmol) and the resulting suspension stirred at ambient temperature for 18 hours. Filtration of the mixture and concentration of the filtrate yields a solid which is purified by silica chromatography (15:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) to provide the title compound as a white solid. MS: m/z (M+1) 435

Step C

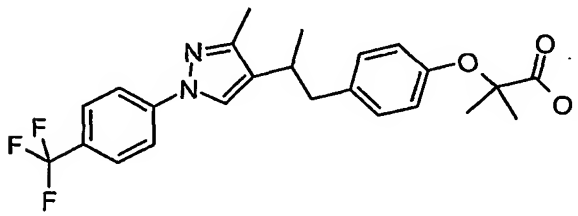
{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid

A solution of {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid methyl ester (120mg, 0.27mmol) in methanol (10ml) is treated with 5N NaOH (0.54ml, 2.7 mmol), and the solution is stirred at ambient temperature for 24 hours. The mixture is concentrated to dryness to give a solid which is dissolved in water (10ml) and ethyl acetate (15ml), and the solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 15ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 421. The structure is also confirmed by proton NMR.

The following compound is prepared substantially as described herein below:

Example 2

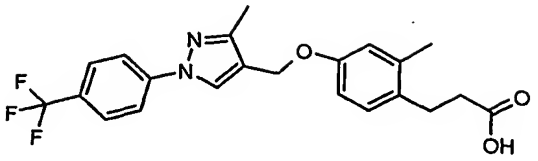
2-Methyl-2-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-propionic acid



HRMS: Calcd. 447.1895, Found: 447.1901.

Example 3

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid



Step A

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester

To a cooled (0°C) solution of [3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (135mg, 0.52mmol) and 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (123mg, 0.63mmol) in tetrahydrofuran (5.0ml) is added tri-n-butylphosphine (0.195ml, 0.78mmol) followed by addition of 1,1'-(azodicarbonyl)dipiperidine (197mg, 0.78mmol) portion-wise over 3 minutes. The mixture is stirred at 0°C for 10 minutes, then removed from the cold bath and stirred for 18 hours. The mixture is diluted with hexanes (10ml), filtered to remove insolubles, and the filtrate concentrated to an oil which is purified by silica flash chromatography (35:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) to provide the title compound as a colorless oil. MS: m/z (M+1) 433.

Step B

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid

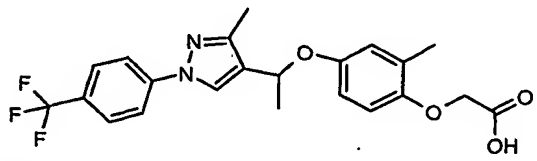
A solution of 3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester (98mg, 0.22mmol) in methanol (3ml) is treated with 5N NaOH (0.11ml, 0.56 mmol), and the solution is stirred at ambient temperature for 18 hours. The mixture is concentrated to dryness to give a solid, which is dissolved in water (10ml) and ethyl acetate (15ml), and the resulting solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 15ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide

the title compound as a white solid. MS: m/z (M+1) 419. The structure is also confirmed by proton NMR.

The following compounds are prepared according to the procedure outlined above in Example 3:

Example 4

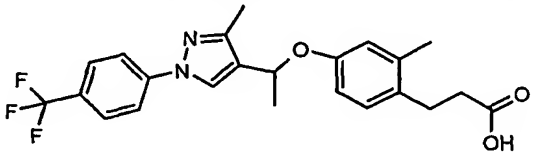
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid



MS: m/z (M+1) 435. The structure is also confirmed by proton NMR.

Example 5

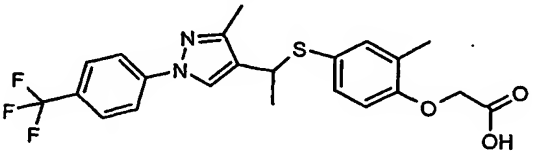
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS: m/z (M+1) 433. The structure is also confirmed by proton NMR.

Example 6

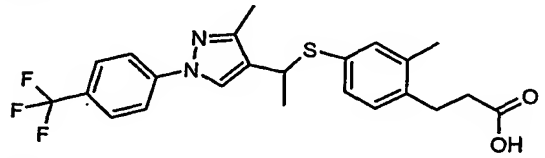
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 7

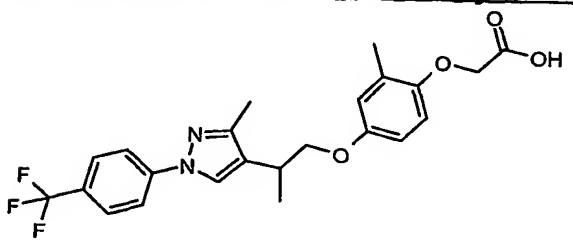
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 8

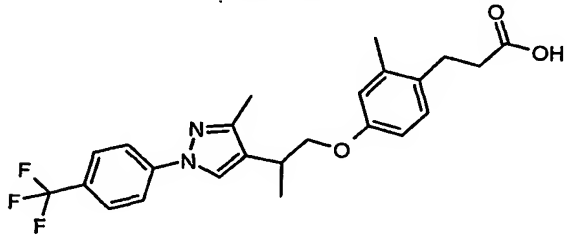
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid



MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 9

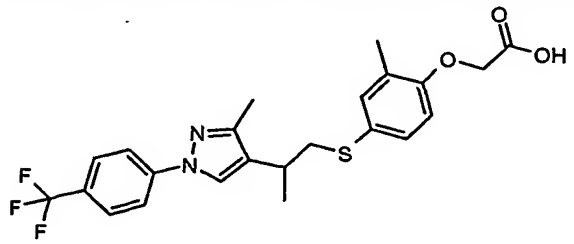
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 10

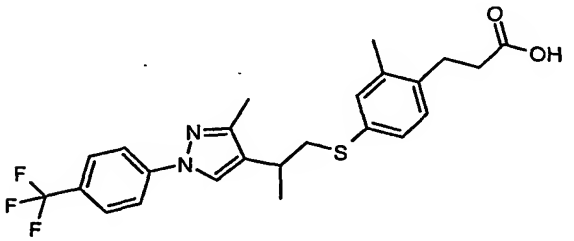
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 11

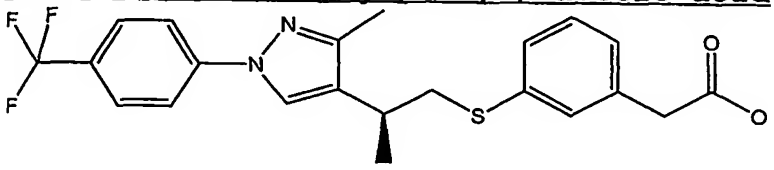
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 12

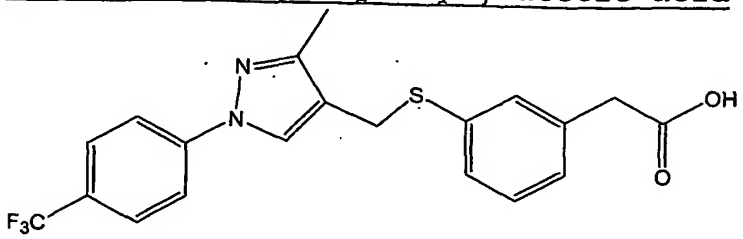
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid



MS (ES): 435 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 13

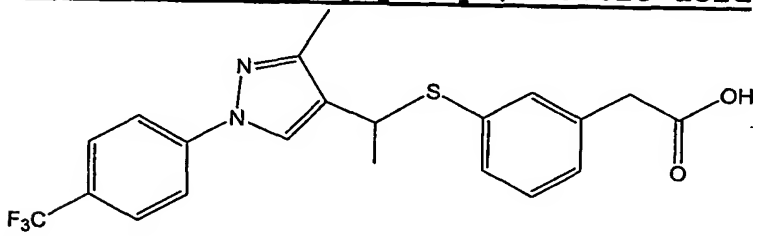
{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid



MS (ES): 407 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 14

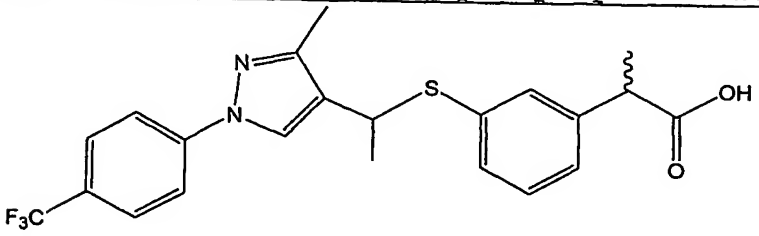
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid



MS (ES): 421 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 15

2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



Step A

Lithium hexamethyldisilazane (0.51 mL, 0.51 mmol) is added dropwise to a solution of(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid methyl ester (0.20 g, 0.46 mmol) in 5 mL THF at -78 C. The resultant solution is stirred for 30 minutes and methyl iodide (0.034 mL, 0.55 mmol) is added

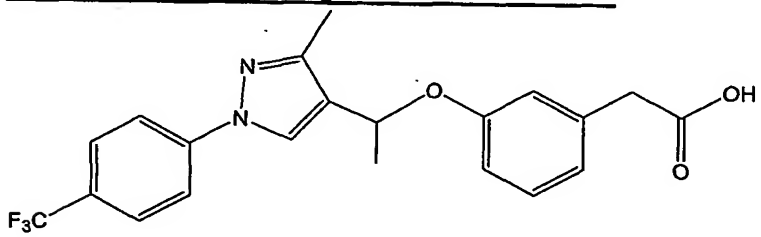
dropwise. The solution is allowed to warm to room temperature over two hours and stirred overnight upon which it is poured into an aqueous solution of NH4Cl. The aqueous layer is extracted with ethyl acetate (3x25mL) and washed with water (25 mL) and brine (25mL). Chromatography (10% ethyl acetate/hexane) provided the ester.

Step B

The ester is hydrolyzed in a similar fashion providing the titled compound. MS (ES) 435 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 16

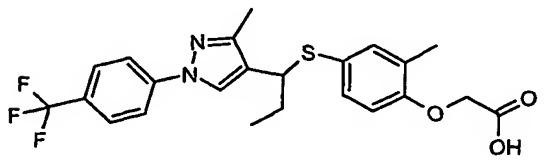
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid



MS (ES): 405 (M^++1). The structure is confirmed by 1H NMR spectroscopy.

Example 17

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



Step A

(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester

Zinc iodide (105mg, 0.33mmol) is added to a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol (185mg, 0.65mmol) and (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (176mg,0.78mmol) in 1,2-dichloroethane (1ml) and the solution stirred at ambient temperature for 1 hour. The mixture is diluted with water (20ml) and dichloromethane (10ml), the organic layer is removed, and the remaining aqueous layer extracted with dichloromethane (2 x 10ml). The combined organic extracts are combined and washed with brine, then dried (Na_2SO_4) and concentrated to an oil which is purified by silica chromatography (15:1 hexanes:ethyl acetate to 10:1 hexanes:ethyl acetate) to give the title compound as a colorless oil. MS: m/z (M+1) 493.

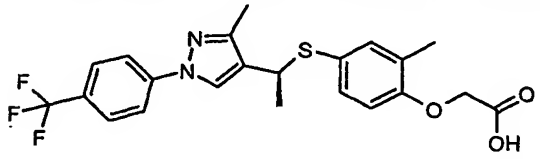
Step B

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid

A solution of (2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester (239mg, 0.48mmol) in methanol (4ml) is treated with 2N NaOH (0.72ml, 1.44 mmol), and the solution is stirred at ambient temperature for 16 hours. The mixture is concentrated to dryness to give a solid, which is dissolved in water (15ml) and ethyl acetate (15ml), and the resulting solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 20ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 18

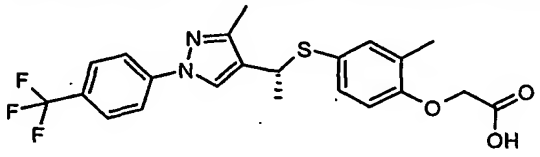
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OD (4.6 x 250mm) column with an eluent consisting of 10% n-propanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 19

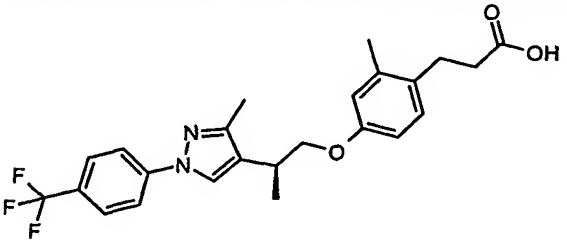
(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OD (4.6 x 250mm) column with an eluent consisting of 10% n-propanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 20

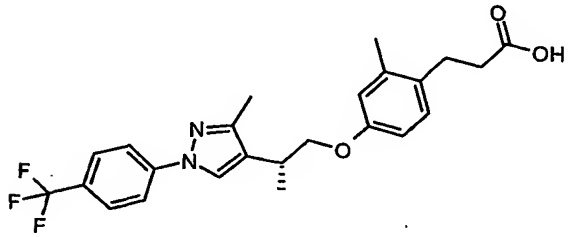
(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 21

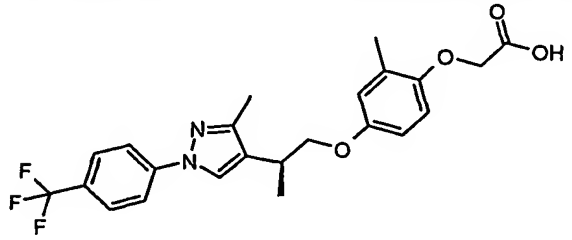
(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 22

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid

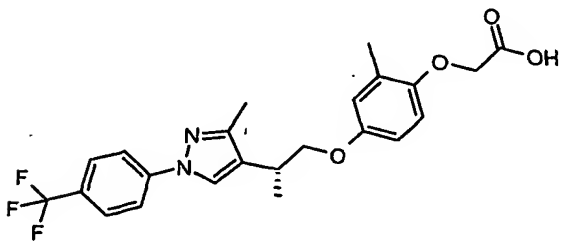


The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first

enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 23

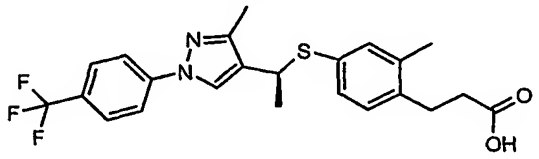
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 24

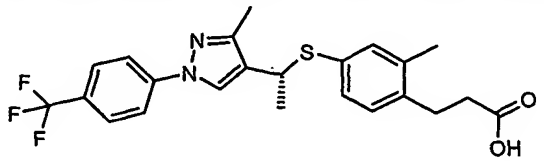
(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 25

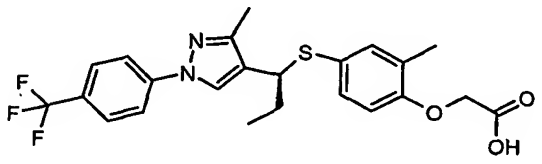
(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 26

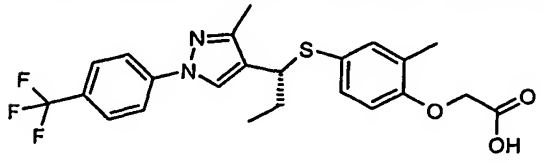
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 10% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 27

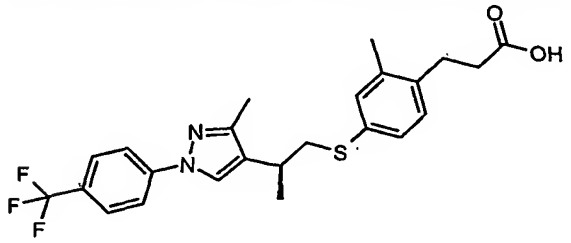
(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 10% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 28

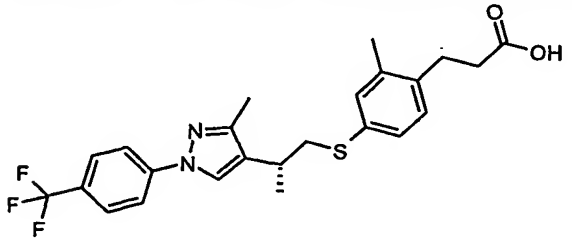
(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 15% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 29

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid

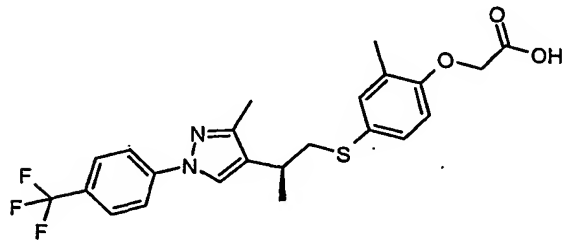


The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 15% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the second

enantiomer. MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 30

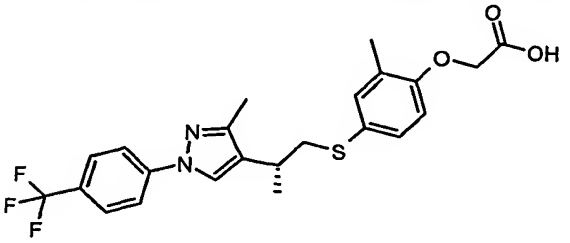
(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OJ (4.6 x 250mm) column with an eluent consisting of 100% ethanol containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 31

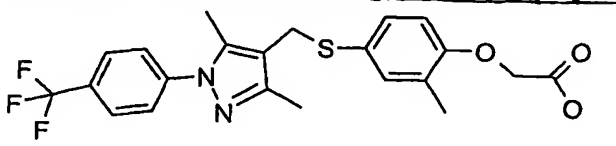
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OJ (4.6 x 250mm) column with an eluent consisting of 100% ethanol containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 32

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



Step A

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

To a solution of 4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (172 mg, 0.6 mmol) and (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (152 mg, 0.67 mmol) in acetonitrile (2.5 mL) is added Ca_2CO_3 (325 mg, 1 mmol). The mixture is stirred at room temperature over night, quenched by water, extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the crude product.

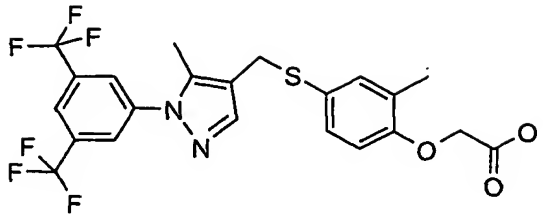
Step B

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

To a solution of {4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester from step A in THF (1 mL is added LiOH (1.0 M, 1 mL). It is stirred at room temperature for 2hrs, is acidified with 5 N HCl, extracted with ether, dried over sodium sulfate. Concentration and reversed phase HPLC purification (acetone/water/TFA as eluent) yields the title compound (62 mg). MS (ES): 453(M^++1); the structure is also confirmed by ^{1}H NMR.

Example 33

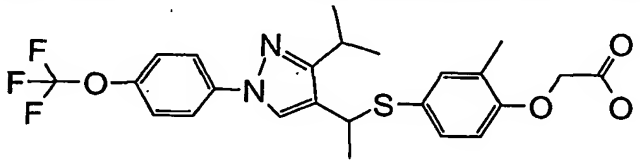
{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 505.1(M^++1); the structure is also confirmed by ^1H NMR.

Example 34

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Step A

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

To a solution of 1-[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethanol (314 mg, 1 mmol) in 1,2-dichloroethane (4 mL) is added ZnI_2 (160 mg, 0.5 mmol), followed by addition of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (270 mg, 0.1.2 mmol). After 2hrs, the reaction mixture is loaded on silica gel column directly and eluted with hexanes/ethyl acetate giving the title compound (498 mg).

Step B

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

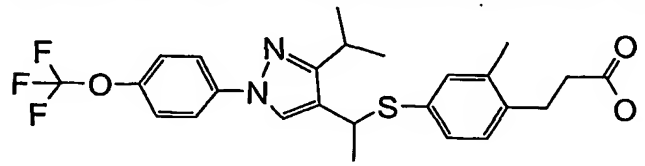
To a solution of (4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (110 mg) from step A in ethanol (1 mL is added NaOH (5.0 M, 1 mL). After stirring at 50 °C for

2hrs, it is acidified with 5 N HCl, extracted with ether, dried over sodium sulfate. Concentration and reversed phase HPLC purification (acetone/water/TFA as eluent) yields the title compound (86 mg). MS (ES): 493.3(M^+-1).

The following compounds are made in a similar manner:

Example 35

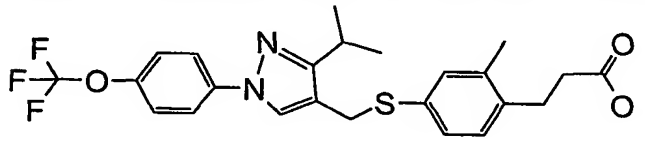
3-(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



MS (ES): 491.3(M^+-1).

Example 36

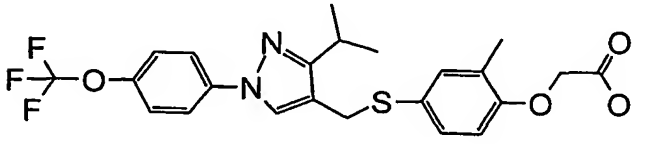
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



MS (ES): 479.1(M^++1).

Example 37

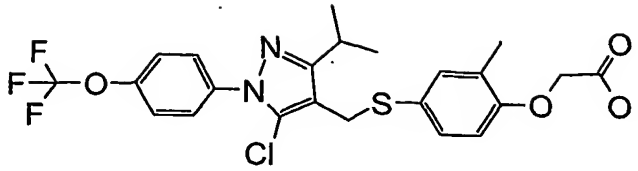
{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 481.1(M^++1).

Example 38

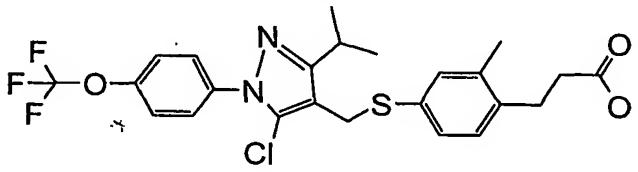
{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 513.1(M^++1, ^{37}Cl).

Example 39

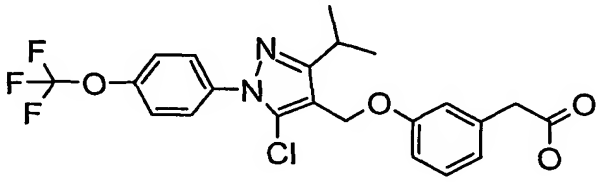
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



MS (ES): 515.1(M^++1, ^{37}Cl).

Example 40

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid



Step A

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid ethyl ester

A solution of [5-chloro-1-(4-difluoromethoxy-phenyl)-3-isopropyl-1H-pyrazol-4-yl]-methanol (100 mg, 0.3 mmol) in toluene (3.0 mL) is degassed and filled with nitrogen for 3 times. 1,1'-(Azodicarbonyl)-dipiperidine (120mg, 0.5 mmol) is added to the reaction mixture under nitrogen at 0 °C, followed by the addition of tributylphosphine (0.124 mL, 0.5 mmol) and (3-hydroxy-phenyl)-acetic acid (83 mg, 0.5 mmol). The reaction mixture is allowed to warm to room temperature and stirred overnight, the mixture is loaded on silica gel column. Chromatography yields the title compound (120 mg).

Step B

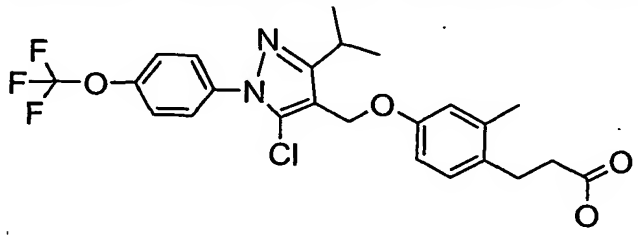
{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid ethyl ester (120 m) from step A is taken into ethanol (1 mL) and treated with NaOH (5.0 N, 1 mL) at 50 °C for 2hrs. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound (120 mg). MS (ES): 469.1(M^+-1), the structure is also confirmed by proton NMR.

The following compounds are made in a similar manner:

Example 41

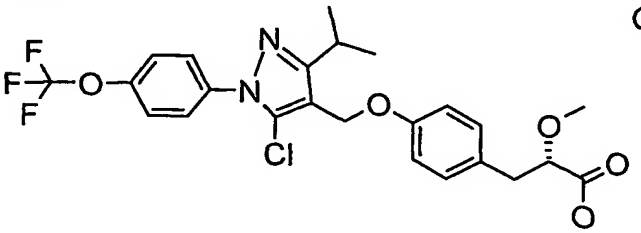
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (ES): 497.1(M^++1), the structure is also confirmed by proton NMR.

Example 42

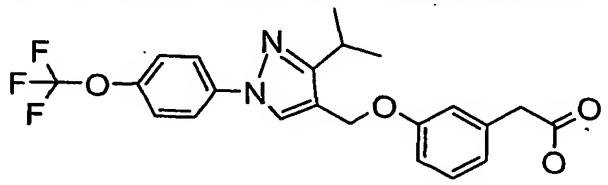
(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid



MS (ES): 513.1(M^++1), the structure is also confirmed by proton NMR.

Example 43

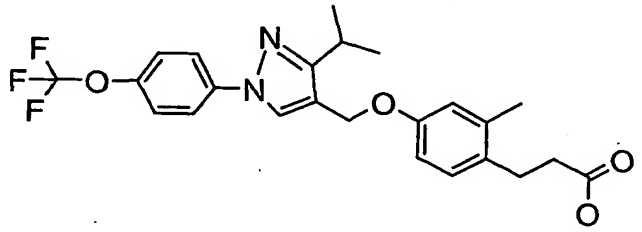
{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 435.5(M^++1), the structure is also confirmed by proton NMR.

Example 44

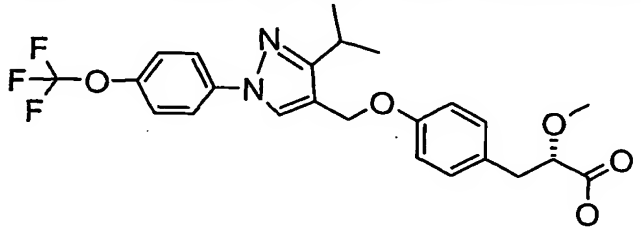
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (ES): 463.4(M^++1), the structure is also confirmed by proton NMR.

Example 45

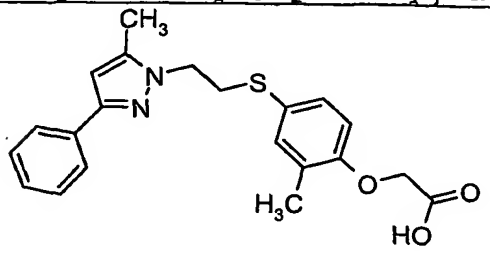
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid



MS (ES): 479.5(M^++1), the structure is also confirmed by proton NMR.

Example 46

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid



Step 1

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (113 mg, 0.500 mmol) is dissolved into anhydrous acetonitrile(ACN) (2 mL). Toluene-4-sulfonic acid 2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethyl ester (176 mg, 0.495 mmol) is added to the reaction, followed by the addition of cesium carbonate (326 mg, 1.00 mmol). The reaction is allowed to stir under nitrogen at room temperature and monitored by TLC and HPLC. Upon complete consumption of the tosylate, the reaction is diluted with diethyl ether and quenched with 0.1N NaOH. The two phases are separated, then the organic layer washed with water and brine. The organic phase is dried over anhydrous sodium sulfate and concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield {2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester (133 mg, 0.346 mmol) or 70%.

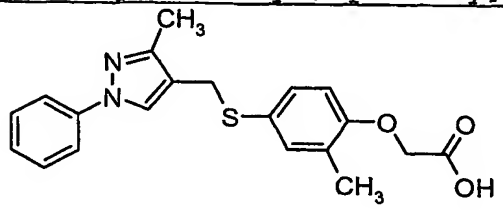
Step 2

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester (133 mg, 0.346 mmol) is dissolved in tetrahydrofuran (1mL) and 1N LiOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 1N HCl (1mL) is added. The mixture is diluted with diethyl ether and extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate.

Concentration of the solvent reveals the pure {2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid in near quantitative yield (130 mg, 0.340 mmol).

Example 47

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid



Step 1

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (113 mg, 0.500 mmol) is dissolved into anhydrous acetonitrile(ACN) (2 mL). Cesium carbonate (326 mg, 1.00 mmol) is added to the reaction, followed by the addition of 4-Chloromethyl-5-methyl-1-phenyl-1H-pyrazole (102 mg, 0.495 mmol). The reaction is allowed to stir under nitrogen at room temperature and monitored by TLC and HPLC. Upon complete consumption of the chloride, the reaction is diluted with diethyl ether and quenched with 0.1N NaOH. The two phases are separated, then the organic layer washed with water and brine. The organic phase is dried over anhydrous sodium sulfate and concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield [2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester (157 mg, 0.396 mmol) or 80%.

Step 2

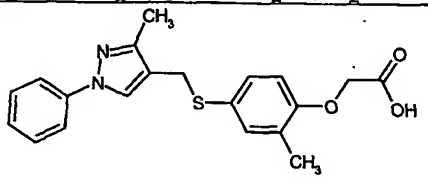
[2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester (157 mg, 0.396 mmol) is dissolved in tetrahydrofuran (1mL) and 1N LiOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 1N HCl (1mL) is

added. The mixture is diluted with diethyl ether and extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate. Concentration of the solvent reveals the pure [2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid in near quantitative yield (138 mg, 0.375 mmol).

The following compounds are made in a substantially similar manner:

Example 48

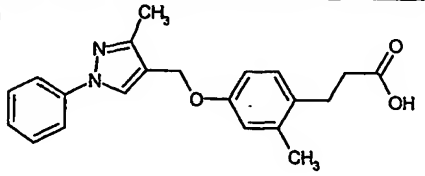
[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid



MS (ES): 351.13 (M^++H).

Example 49

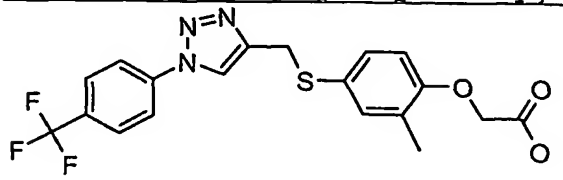
3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid



MS (ES): 369.04 (M^++H).

Example 50

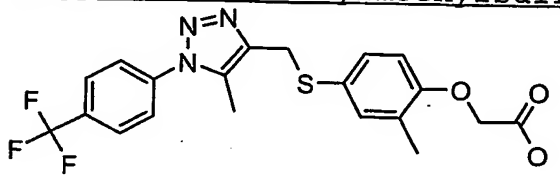
{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 424.4 (M^++H).

Example 51

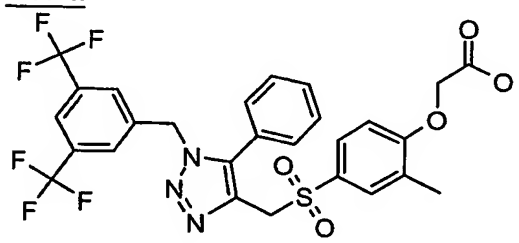
{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 438.4 (M^++H).

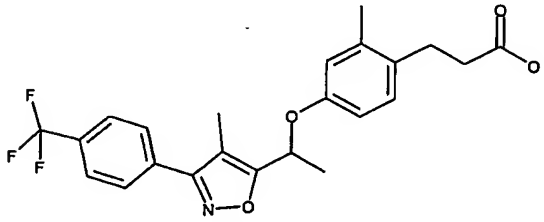
Example 52

{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 614.5 (M^++H).

Example 53



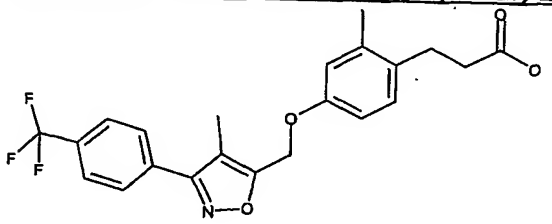
3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid

A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (88 mg, 0.45 mmol) and 1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol (81 mg, 0.30 mmol) in toluene (10 mL) is degassed and filled with nitrogen for 3 times. Tributylphosphine (91 mg, 0.45 mmol) is added to the reaction mixture under nitrogen at 0 °C,

followed by addition of of 1,1'-(azodicarbonyl)-dipiperidine (88 mg, 0.45 mmol). The reaction mixture is allowed to warm to room temperature and stirred for 48 hours. The mixture is loaded directly on silica gel chromatography with 25% EtOAc/Hexanes to obtain the intermediate ester. This intermediate is taken into THF (0.5 mL) and MeOH 1.0 mL), and is treated with NaOH (2.0 N, 1.5 mL) for 2 hours. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound (21 mg, 16%). MS (ES): 434.3; the structure is also confirmed by proton NMR.

Example 54

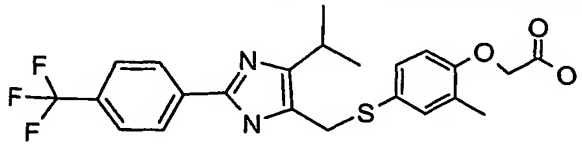
3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid



MS (ES): 420.2; the structure is also confirmed by proton NMR.

Example 55

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



Step A

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (120 mg, 0.53 mmol) and [5-isopropyl-2-(4-

trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol (100 mg, 0.35 mmol) in toluene (3.0 mL) is degassed and filled with nitrogen for 3 times. Tributylphosphine (0.13 mL) is added to the reaction mixture under nitrogen at 0 °C, followed by addition of of 1,1'-(azodicarbonyl)-dipiperidine (134 mg). The reaction mixture is allowed to warm to room temperature and stirred overnight, the mixture is loaded on silica gel column. Chromatography yields the title compound (120 mg).

Step B

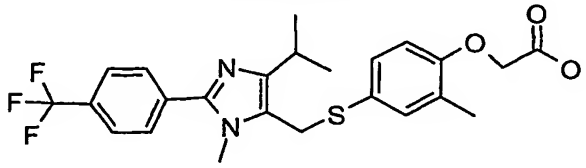
{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

({4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (120 mg) is taken into THF (2 mL) and treated with LiOH (1.0 N, 2 mL) for 2hrs. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound. MS (ES): 465.2(M^++1), the structure is also confirmed by proton NMR.

The following compounds are made in a similar manner:

Example 56

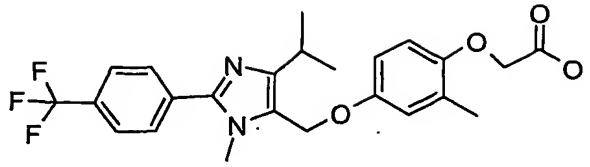
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 477.2(M^+-1), the structure is also confirmed by proton NMR.

Example 57

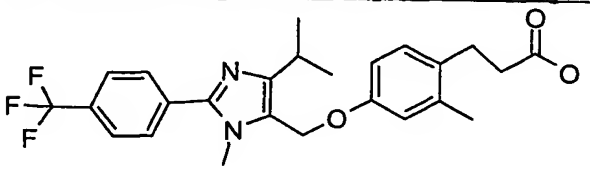
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenoxy}-acetic acid



MS (ES): 463.2(M^++1), the structure is also confirmed by proton NMR.

Example 58

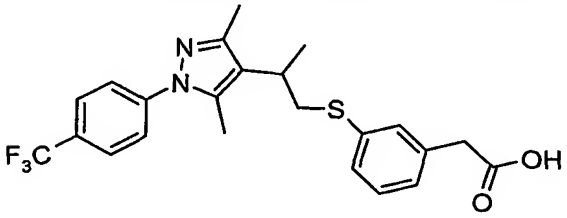
3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (ES): 461.2(M^++1), the structure is also confirmed by proton NMR.

Example 59

(3-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid



Step A

(3-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid methyl ester

Dissolve 2-[3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol (219 mg. 0.74 mmol) in toluene (20 mL). Add (3-mercapto-phenyl)-acetic acid methyl ester (175 mg., 0.96 mmol) while stirring. This mixture is degassed passing Argon for 10 minutes. Then, add n-tributyl phosphine (0.3 mL, 1.18 mmol) dropwise. Cool the reaction mixture to 0°C (ice bath). Add Azo-dicarbonyldipiperidine (ADDP) (261

mg., 1.04 mmol) portionwise. Allow the reaction mixture to warm slowly to room temperature overnight. The next day, remove the solvent on rotavapor. Take up the resulting solid in ethyl ether (70 mL), filter off the solids and wash the filtrate with saturated sodium bicarbonate solution (3x 30 mL), brine (3x 30 mL), dry over Na_2SO_4, and concentrate to afford the crude compound. Purify by silica gel column chromatography (40% EtOAc in Hexanes) to yield 330 mg. of pure title compound (97%). MPLC ($M^+ + 1 = 463.3$).

Step B

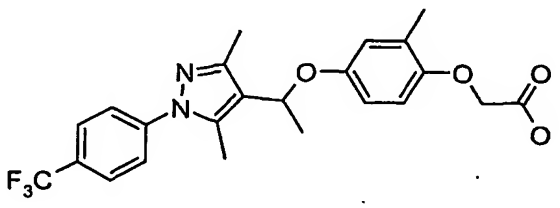
(3-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid

Dissolve (3-{2-[3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl) acetic acid methyl ester (114 mg., 0.25 mmol) in THF (5 ml) and MeOH (10 mL) at room temperature. Cool to 0°C (ice bath) and add 2.5 mL of a 2N aqueous solution of KOH. Stir the reaction at room temperature overnight. The following day, add 2N HCl until the solution reach pH=3-4. Extract with EtOAc (70 mL), wash the organic phase with brine (3x 30 mL), and dry over Na_2SO_4 to afford 110 mg. of title compound (99%). MPLC ($M^+ + 1 = 449.3$).

The following compounds were made in a similar manner:

Example 60

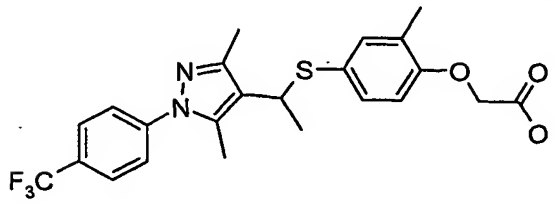
(4-{1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-2-methyl-phenoxy)-acetic acid



MS ($M^+ + 1 = 449.1$).

Example 61

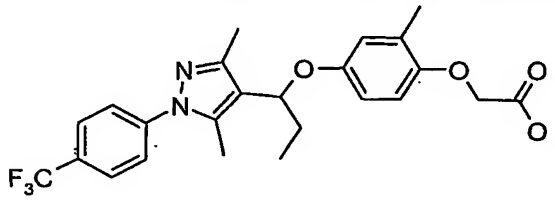
(4-{1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



MS ($M^+ + 1 = 465.1$).

Example 62

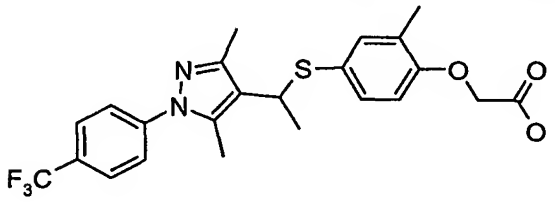
(4-{1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenoxy)-acetic acid



MS ($M^+ + 1 = 463.1$).

Example 63

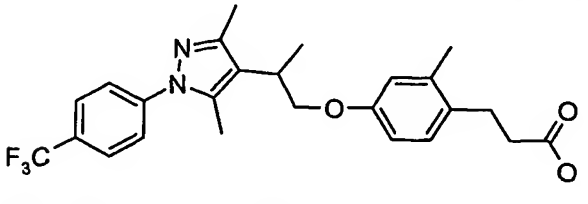
(4-{1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid



MS ($M^+ + 1 = 478.1$).

Example 64

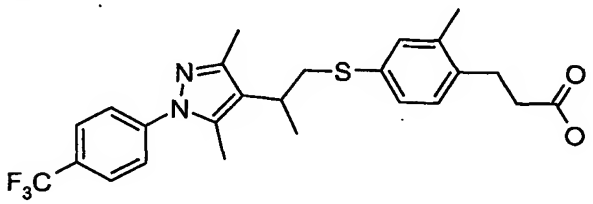
3-(4-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenyl)-propionic acid



MS ($M^+ + 1 = 461.1.1$).

Example 65

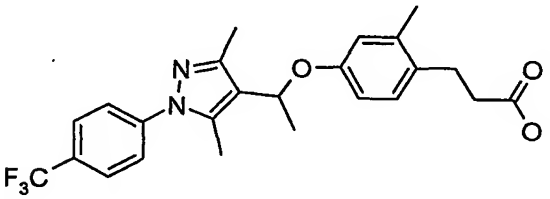
3-(4-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-2-methyl-phenyl)-propionic acid



MS (M^+ + 1 = 477.1).

Example 66

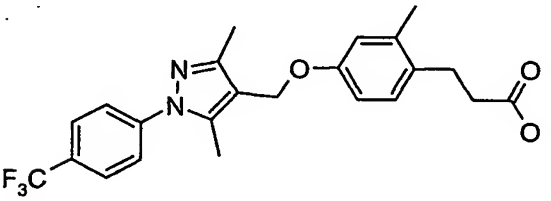
3-(4-{1-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-2-methyl-phenyl)-propionic acid



MS (M^+ + 1 = 447.1).

Example 67

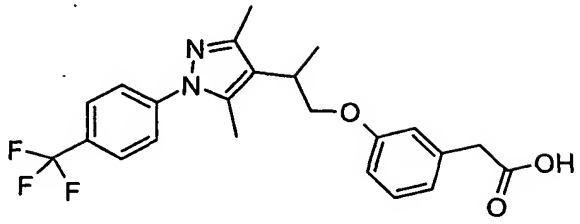
3-{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (M^+ + 1 = 433.1).

Example 68

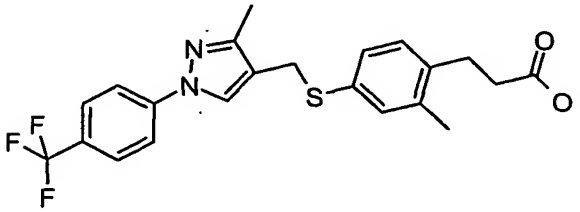
(3-{2-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-acetic acid



MS (M^+ + 1 = 433.1).

Example 69

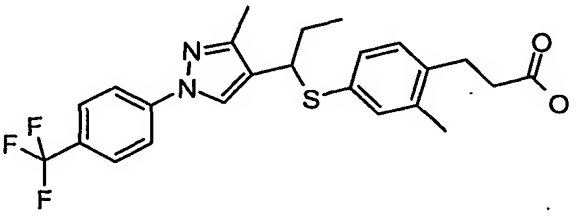
3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



HRMS: Calcd.435.1354, Found: 435.1351.

Example 70

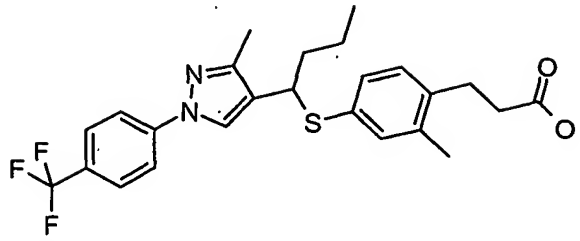
3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



HRMS: Calcd.463.1667, Found: 463.1651.

Example 71

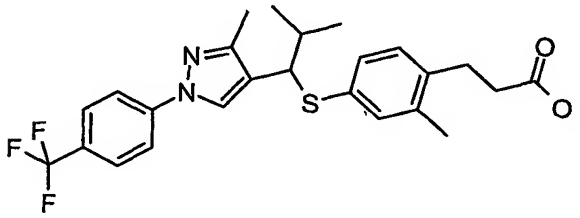
3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-propionic acid



HRMS: Calcd.477.1823, Found: 477.1825.

Example 72

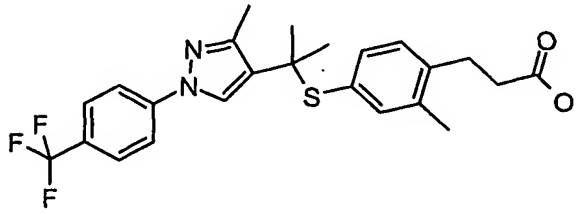
3-(2-Methyl-4-{2-methyl-1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



HRMS: Calcd.477.1823, Found: 477.1817

Example 73

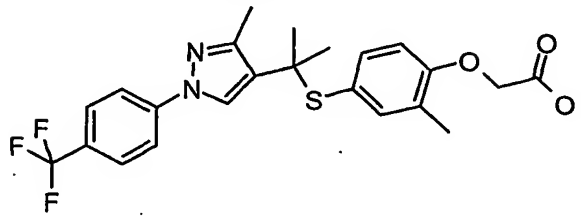
3-(2-Methyl-4-{1-methyl-1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



HRMS: Calcd.463.1667, Found: 463.1654.

Example 74

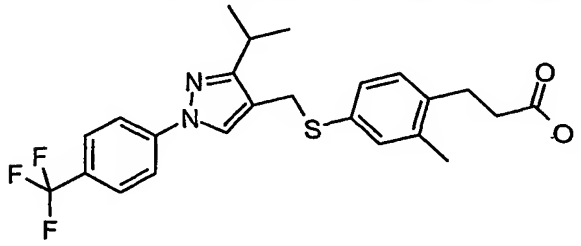
(2-Methyl-4-{1-methyl-1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



HRMS: Calcd.465.1460, Found: 465.1444

Example 75

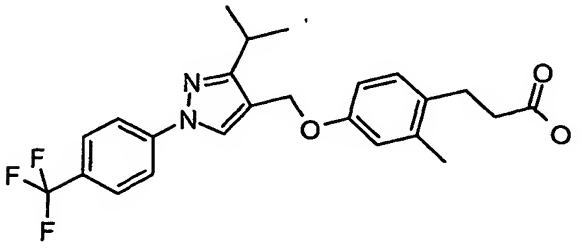
3-{4-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



HRMS: Calcd.463.1667, Found: 463.1669.

Example 76

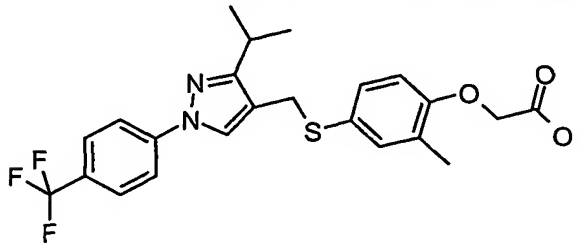
3-{4-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



HRMS: Calcd.447.1895, Found: 447.1893.

Example 77

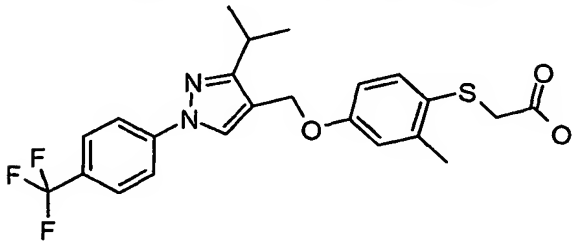
{4-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



HRMS: Calcd. 465.1460, Found: 465.1439.

Example 78

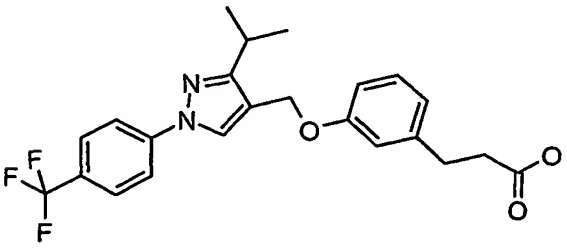
{4-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenylsulfanyl}-acetic acid



HRMS: Calcd. 465.1460, Found: 465.1451

Example 79

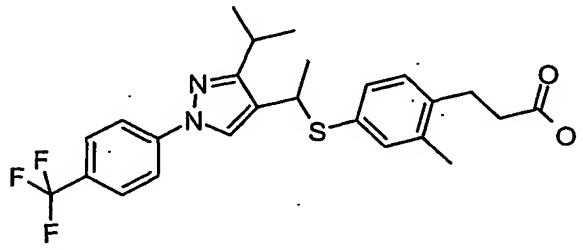
3-{3-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid



HRMS: Calcd. 433.1739, Found: 433.1736.

Example 80

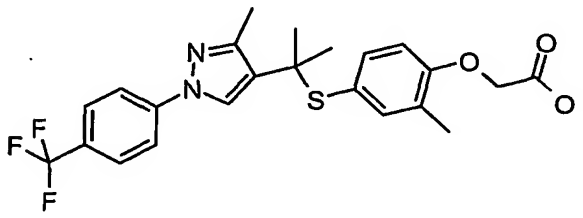
3-(4-{1-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



HRMS: Calcd. 477.1823, Found: 477.1820.

Example 81

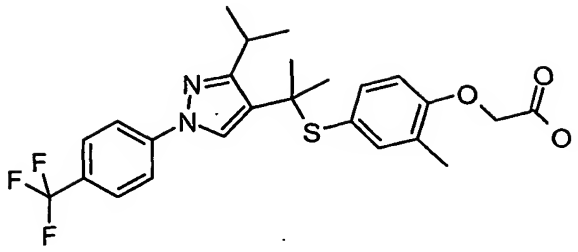
3-(4-{1-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-methyl-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



HRMS: Calcd. 491.1980, Found: 491.1977.

Example 82

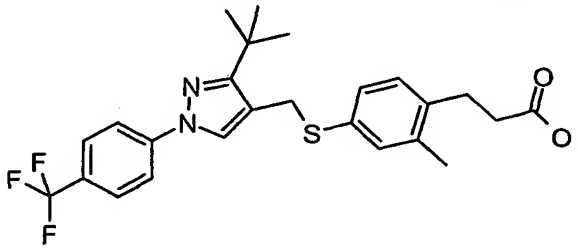
(4-{1-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-1-methyl-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



HRMS: Calcd. 493.1773, Found: 493.1762.

Example 83

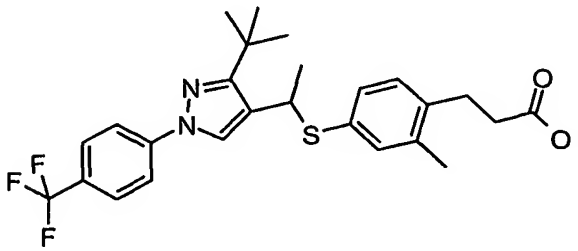
3-{4-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



HRMS: Calcd. 477.1823, Found: 477.1810.

Example 84

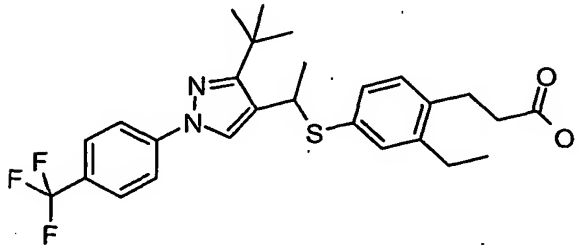
3-(4-{1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



HRMS: Calcd. 491.1980, Found: 491.1970.

Example 85

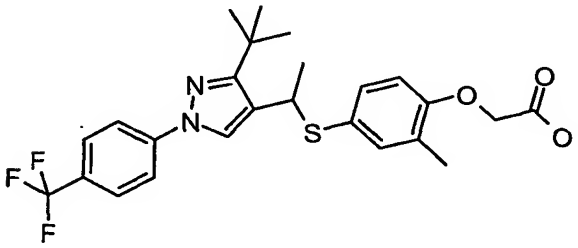
3-(4-{1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-ethyl-phenyl)-propionic acid



HRMS: Calcd. 505.2137, Found: 505.2125.

Example 86

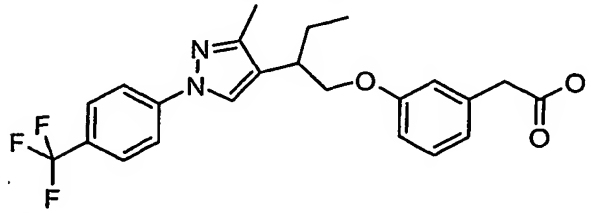
(4-{1-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



HRMS: Calcd. 493.1773, Found: 493.1779.

Example 87

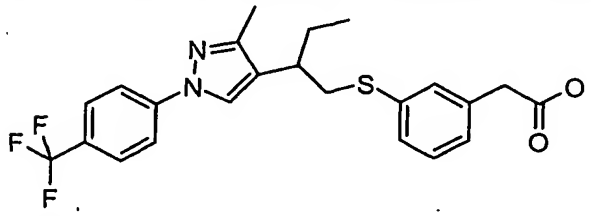
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenyl)-acetic acid



HRMS: Calcd. 433.1739, Found: 433.1745.

Example 88

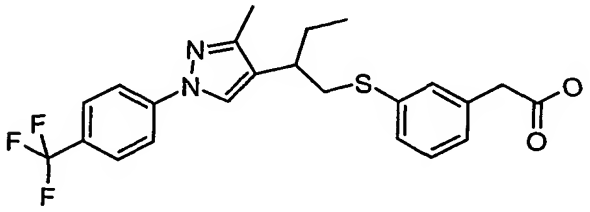
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-acetic acid



HRMS: Calcd. 449.1511, Found: 449.1502.

Example 89

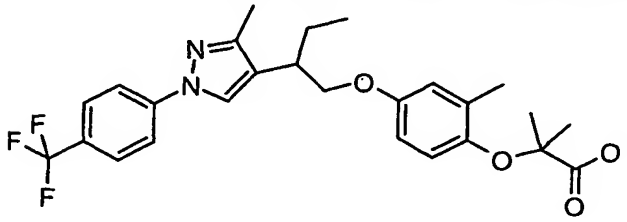
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-acetic acid



Isomer-1, HRMS: Calcd. 449.1511, Found: 449.1517;
Isomer-2, HRMS: Calcd. 449.1511, Found: 449.1514.

Example 90

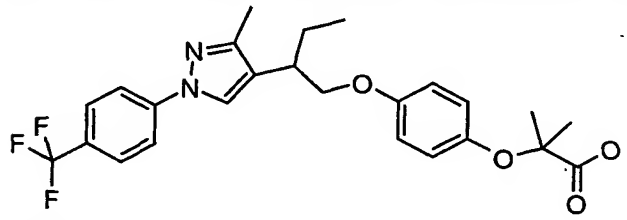
2-Methyl-2-(2-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenoxy)-propionic acid



HRMS: Calcd. 491.2158, Found: 491.2137.

Example 91

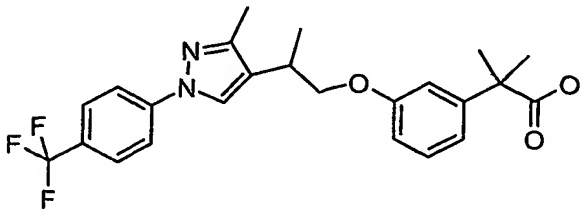
2-Methyl-2-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenoxy)-propionic acid



HRMS: Calcd. 477.2001, Found: 477.1977.

Example 92

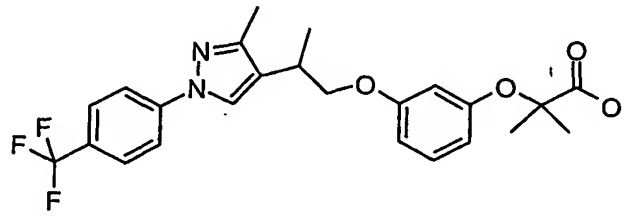
2-Methyl-2-(3-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



HRMS: Calcd. 447.1895, Found: 447.1882.

Example 93

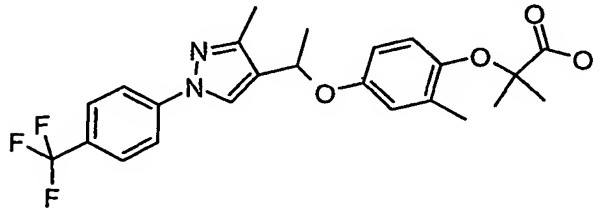
2-Methyl-2-(3-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-propionic acid



HRMS: Calcd. 463.1844, Found: 463.1824.

Example 94

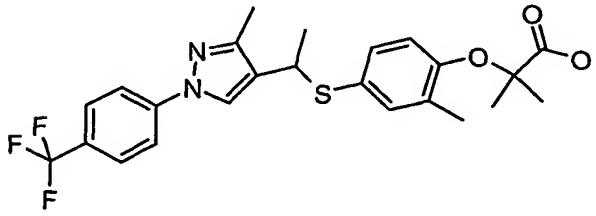
2-Methyl-2-(2-methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-propionic acid



ESMS+: 463 (M+H).

Example 95

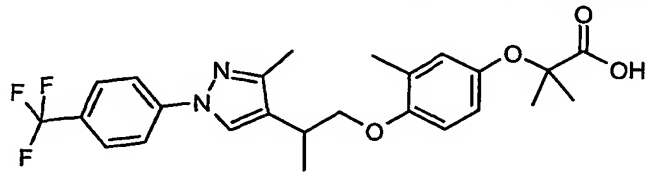
2-Methyl-2-(2-methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-propionic acid



HRMS: Calcd. 479.1616, Found, 479.1618.

Example 96

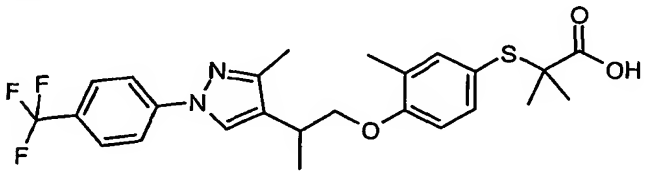
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-propionic acid



High Res. EI-MS: 463.1827; calc.463.1844.

Example 97

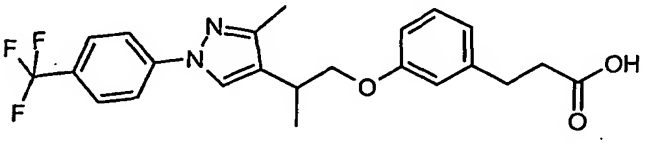
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenylsulfanyl)-propionic acid



High Res. EI-MS: 493.1757; calc.493.1773.

Example 98

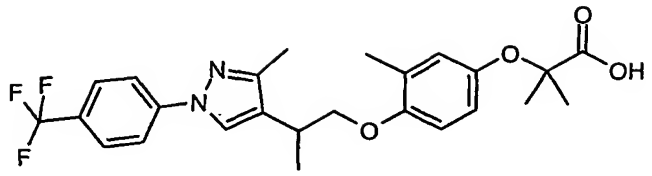
3-(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



High Res. EI-MS: 433.1724; calc.493.1739.

Example 99

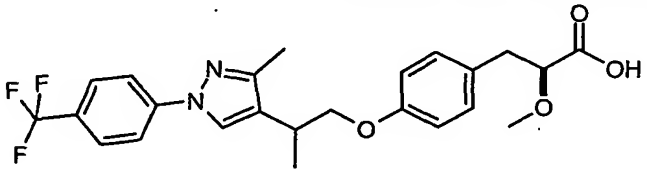
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-propionic acid



High Res. EI-MS: 477.1998; calc.477.2001.

Example 100

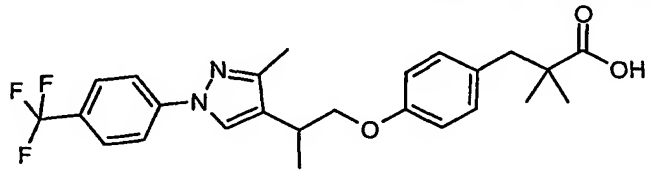
2-Methoxy-3-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



High Res. EI-MS: 463.1837; calc.463.1844.

Example 101

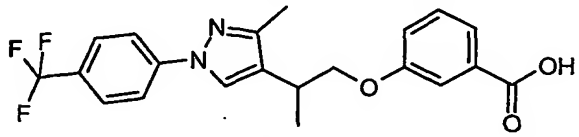
2,2-Dimethyl-3-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



High Res. EI-MS: 475.2201; calc.475.2208.

Example 102

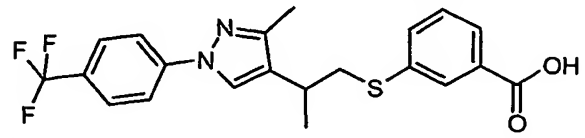
3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-benzoic acid



High Res. EI-MS: 405.1428; calc.405.1426.

Example 103

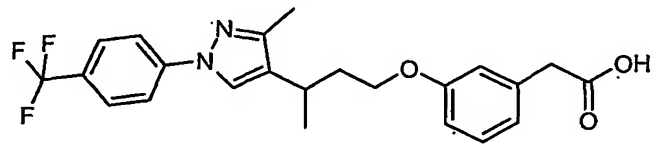
3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-benzoic acid



High Res. EI-MS: 421.1209; calc.421.1198.

Example 104

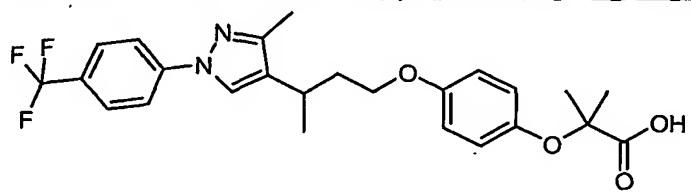
(3-{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenyl)-acetic acid



High Res. EI-MS: 433.1729; calc.433.1739.

Example 105

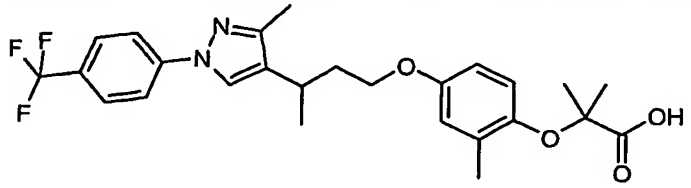
2-Methyl-2-(4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenoxy)-propionic acid



High Res. EI-MS: 477.1998; calc.477.2001.

Example 106

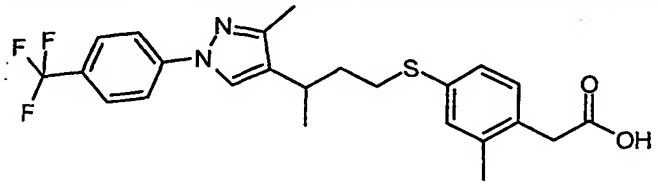
2-Methyl-2-(2-methyl-4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenoxy)-propionic acid



High Res. EI-MS: 491.2146; calc.491.2158.

Example 107

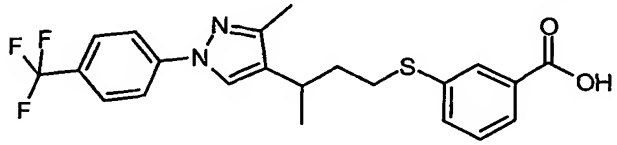
(2-Methyl-4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-acetic acid



High Res. EI-MS: 479.1605; calc.479.1616.

Example 108

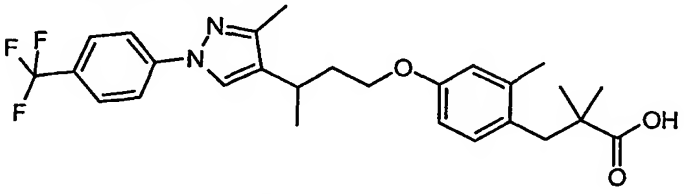
3-{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-benzoic acid



High Res. EI-MS: 435.1348; calc.435.1354.

Example 109

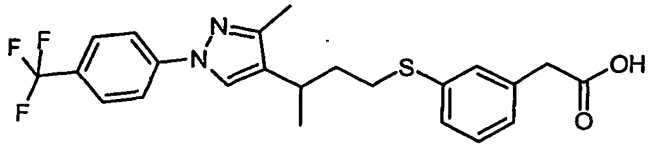
2,2-Dimethyl-3-(2-methyl-4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenyl)-propionic acid



High Res. EI-MS: 489.2325; calc.489.2365.

Example 110

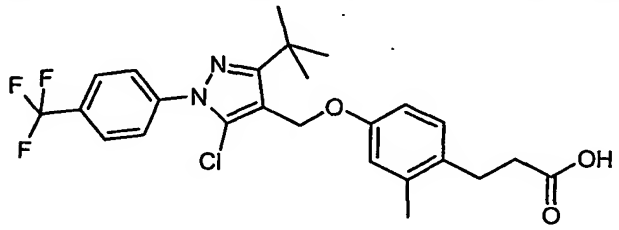
(3-{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-acetic acid



High Res. EI-MS: 449.1524; calc.449.1511.

Example 111

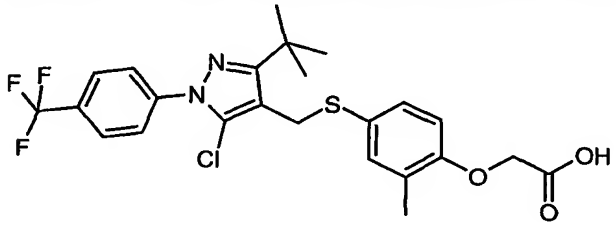
3-{4-[3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



High Res. EI-MS: 495.1656; calc.495.1662.

Example 112

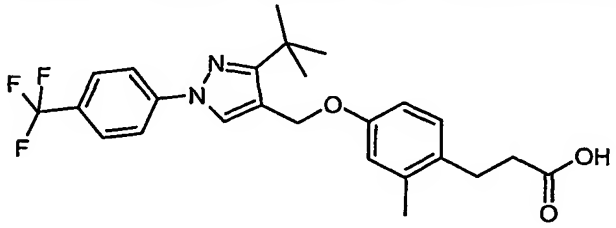
{4-[3-tert-Butyl-5-chloro-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



High Res. EI-MS: 513.1224; calc.513.1226.

Example 113

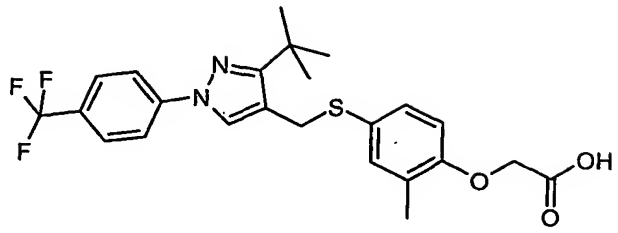
3-{4-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (ES): 461.2 (M+1)

Example 114

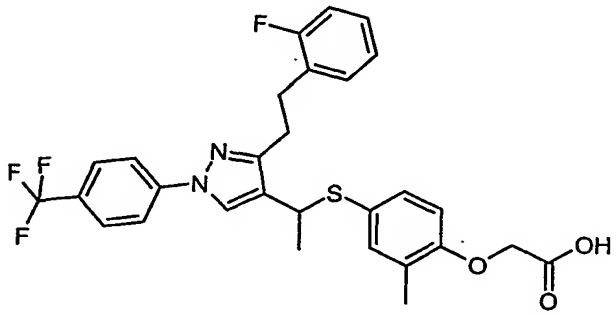
{4-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 479.2 (M+1)

Example 115

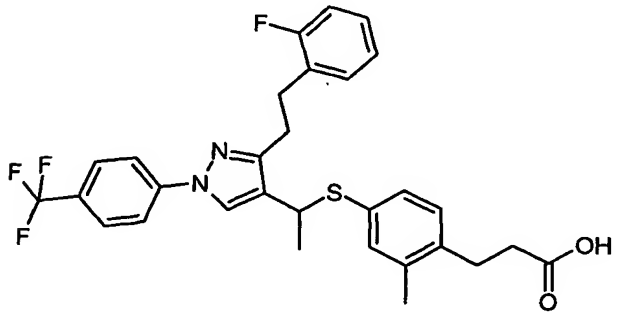
(4-{1-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



High Res. EI-MS: 559.1672; calc.559.1678.

Example 116

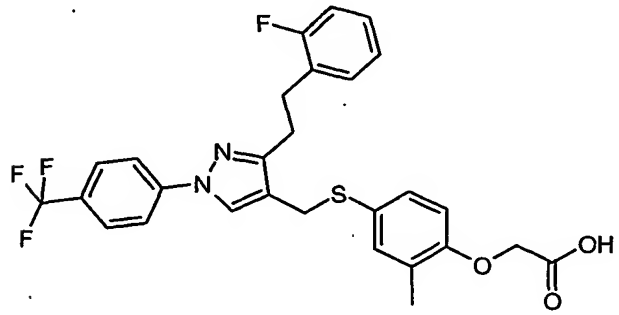
3-(4-{1-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid



High Res. EI-MS: 557.1864; calc.557.1866.

Example 117

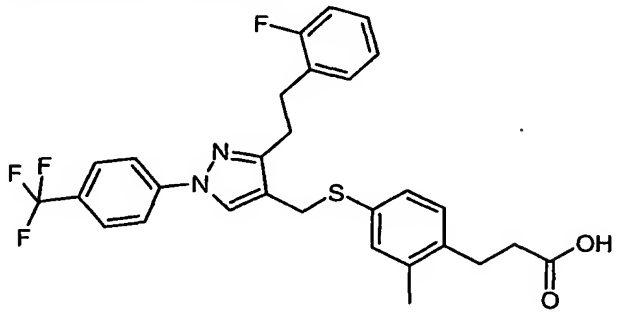
{4-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



High Res. EI-MS: 545.1512; calc.545.1522.

Example 118

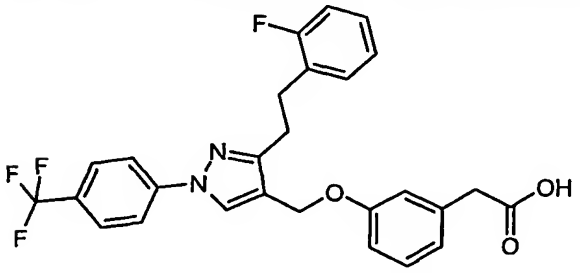
3-{4-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



High Res. EI-MS: 543.1706; calc.543.1729.

Example 119

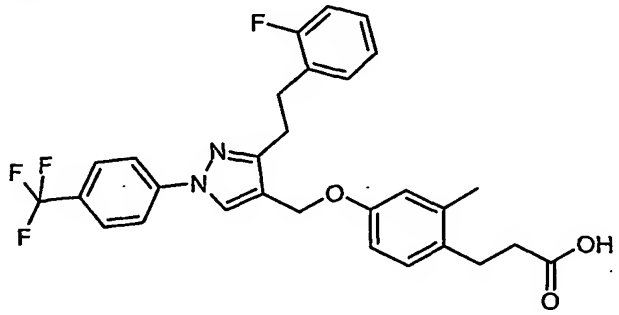
{3-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxyl-phenyl}-acetic acid



High Res. EI-MS: 499.1647; calc.499.1645.

Example 120

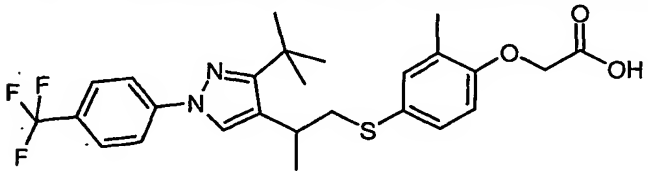
3-{4-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



High Res. EI-MS: 527.1953; calc.527.1957.

Example 121

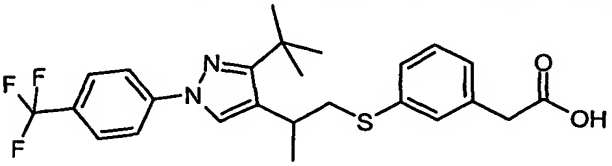
(4-{2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-2-methyl-phenoxy)-acetic acid



High Res. EI-MS: 507.1917; calc.507.1929.

Example 122

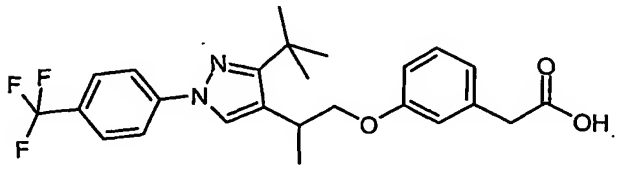
(3-{2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid



High Res. EI-MS: 461.2061; calc.461.2025.

Example 123

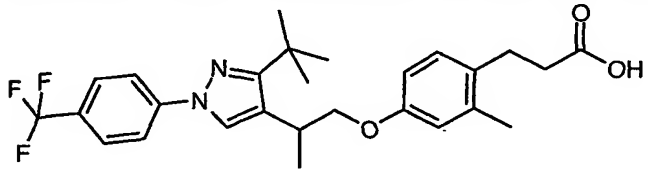
(3-{2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-acetic acid



High Res. EI-MS: 447.1830; calc.447.1823.

Example 124

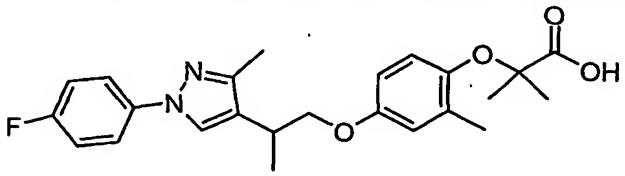
3-(4-{2-[3-tert-Butyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenyl)-propionic acid



High Res. EI-MS: 489.2371; calc.489.2365.

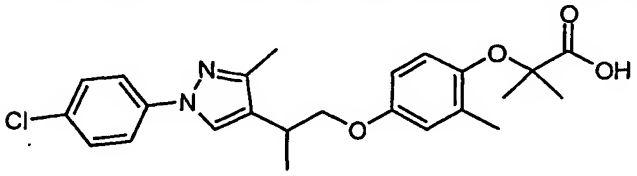
Example 125

2-(4-{2-[1-(4-Fluoro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



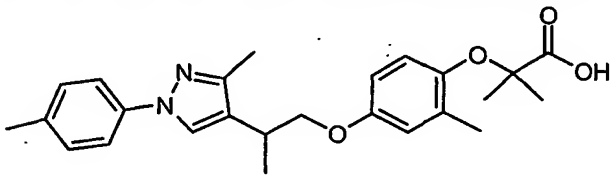
Example 126

2-(4-{2-[1-(4-Chloro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



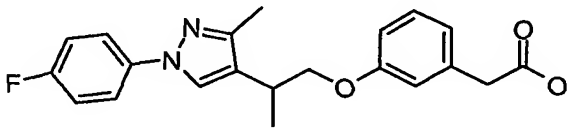
Example 127

2-Methyl-2-{2-methyl-4-[2-(3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-propoxy]-phenoxy}-propionic acid



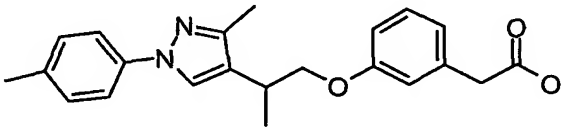
Example 128

(3-{2-[1-(4-Fluoro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-phenyl)-acetic acid



Example 129

{3-[2-(3-Methyl-1-p-tolyl-1H-pyrazol-4-yl)-propoxy]-phenyl}-acetic acid

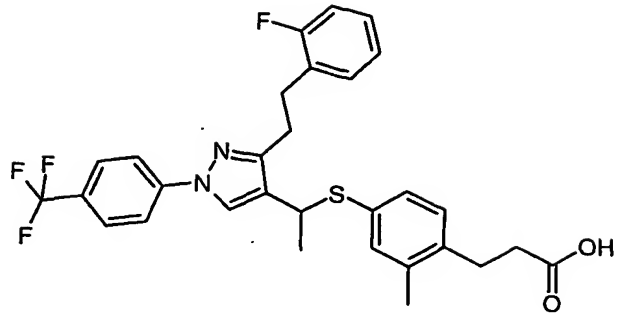


The following single enantiomers were obtained by chiral separation using chiral HPLC column:

Example 130

3-(4-{1-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

Chiral

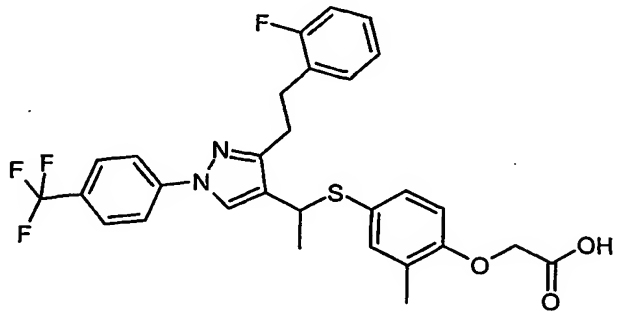


Isomer 1, High Res. EI-MS: 557.1886; calc.557.1866.
Isomer 2, High Res. EI-MS: 557.1922; calc.557.1866.

Example 131

(4-{1-[3-[2-(2-Fluoro-phenyl)-ethyl]-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

Chiral

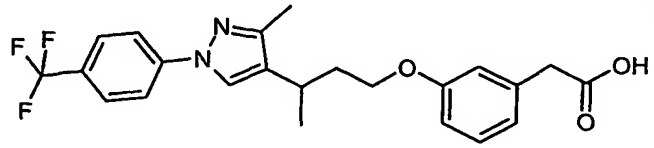


Isomer 1, High Res. EI-MS: 559.1665; calc.559.1678.
Isomer 2, High Res. EI-MS: 559.1666; calc.559.1678.

Example 132

(3-{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenyl)-acetic acid

Chiral

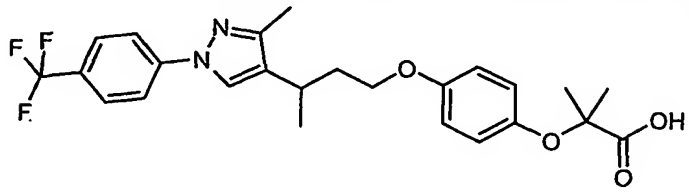


Isomer 1, High Res. EI-MS: 433.1728; calc.433.1739.
Isomer 2, High Res. EI-MS: 433.1732; calc.433.1739.

Example 133

2-Methyl-2-(4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenoxy)-propionic acid

Chiral

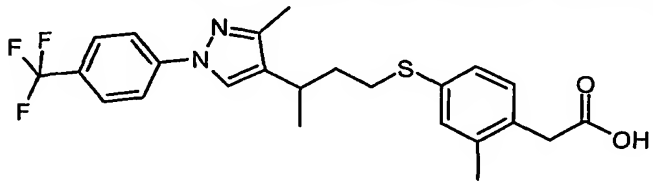


Isomer 1, High Res. EI-MS: 477.1986; calc.477.2001.
Isomer 2, High Res. EI-MS: 477.1985; calc.477.2001.

Example 134

(2-Methyl-4-{3-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butylsulfanyl}-phenyl)-acetic acid

Chiral

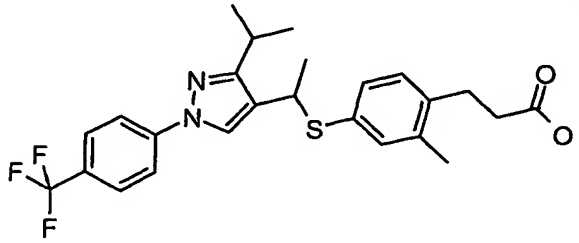


Isomer 1, High Res. EI-MS: 479.1611; calc.479.1616.
Isomer 2, High Res. EI-MS: 479.1610; calc.479.1616.

Example 135

3-(4-{1-[3-Isopropyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid

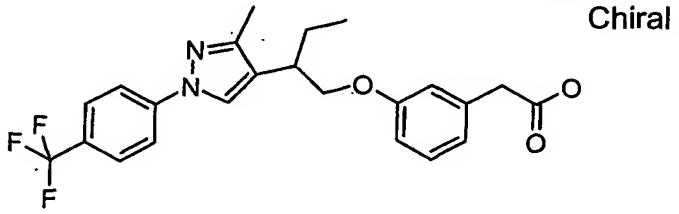
Chiral



Isomer-1: HRMS: Calcd. 477.1823, Found: 477.1810;
Isomer-2: HRMS: Calcd. 477.1823, Found: 477.1812.

Example 136

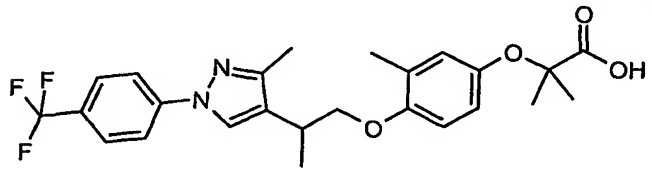
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-butoxy}-phenyl)-acetic acid



Isomer-1, ESMS+: 433 (M+H);
Isomer-2, ESMS+: 433 (M+H).

Example 137

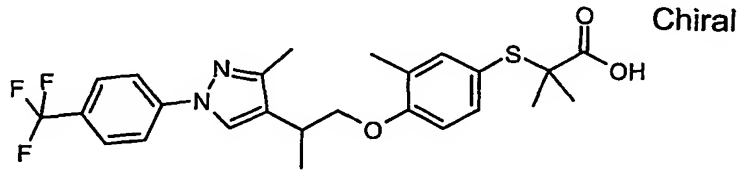
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-propionic acid



Isomer 1; High Res. EI-MS: 463.1886; calc.463.1844.
Isomer 2, High Res. EI-MS: 463.1839; calc.463.1844.

Example 138

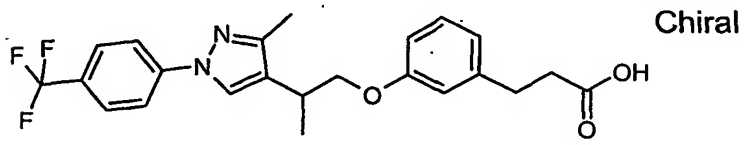
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenylsulfanyl)-propionic acid



Isomer 1, High Res. EI-MS: 493.1785; calc.493.1773.
Isomer 2, High Res. EI-MS: 493.1757; calc.493.1773.

Example 139

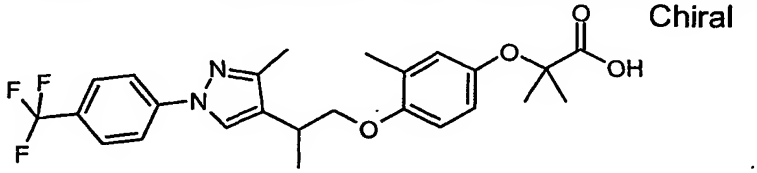
3-(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



Isomer 1, High Res. EI-MS: 433.1745; calc.493.1739.
Isomer 2, High Res. EI-MS: 433.1719; calc.493.1739.

Example 140

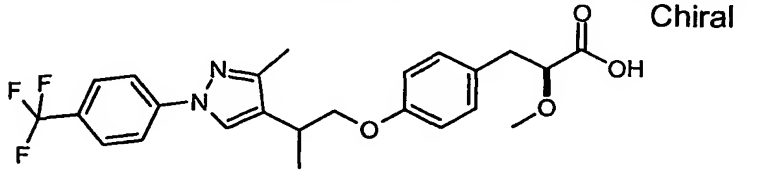
2-Methyl-2-(3-methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-propionic acid



Isomer 1, High Res. EI-MS: 477.1989; calc.477.2001.
Isomer 2, High Res. EI-MS: 477.1989; calc.477.2001.

Example 141

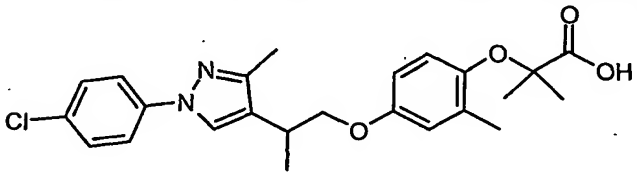
2-Methoxy-3-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



Isomer 1, High Res. EI-MS: 463.1838; calc.463.1844.
Isomer 2, High Res. EI-MS: 463.1854; calc.463.1844.

Example 142

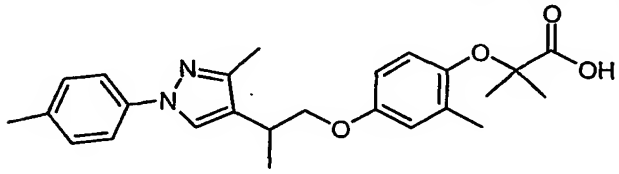
2-(4-{2-[1-(4-Chloro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



Isomer-1 and Isomer-2.

Example 143

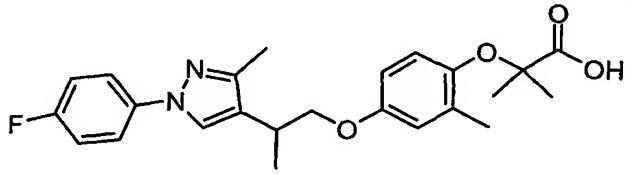
2-Methyl-2-{2-methyl-4-[2-(3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-propoxy]-phenoxy}-propionic acid



Isomer-1: and Isomer-2.

Example 144

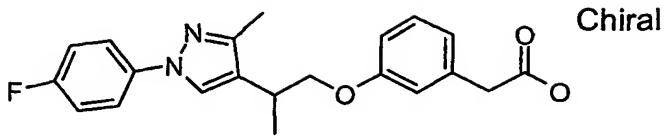
2-(4-{2-[1-(4-Fluoro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



Isomer-1 and Isomer-2.

Example 145

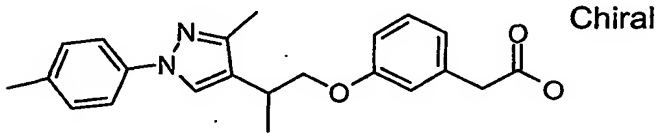
(3-{2-[1-(4-Fluoro-phenyl)-3-methyl-1H-pyrazol-4-yl]-propoxy}-phenyl)-acetic acid



Isomer-1 and Isomer-2.

Example 146

{3-[2-(3-Methyl-1-p-tolyl-1H-pyrazol-4-yl)-propoxy]-phenyl}-acetic acid

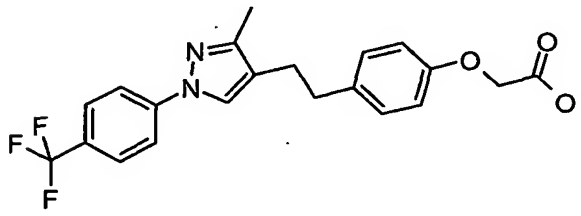


Isomer-1 and Isomer-2.

The following compounds were also made:

Example 147

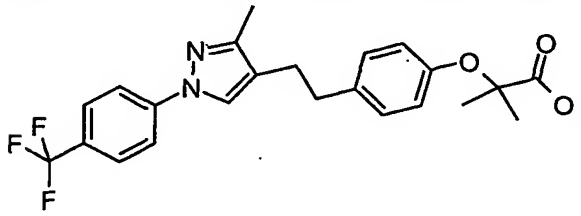
(4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethyl}-phenoxy)-acetic acid



HRMS: Calcd. 405.1426, Found: 405.1412.

Example 148

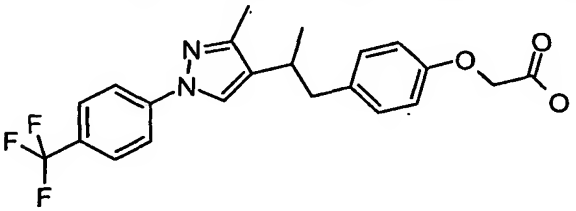
2-Methyl-2-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethyl}-phenoxy)-propionic acid



HRMS: Calcd. 433.1739, Found: 433.1731.

Example 149

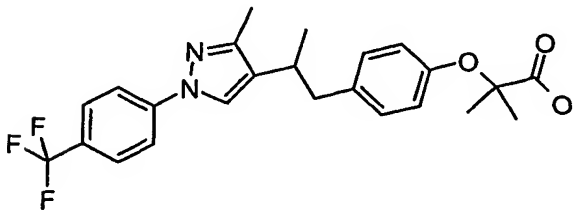
(4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-acetic acid



HRMS: Calcd. 419.1582, Found: 419.1594.

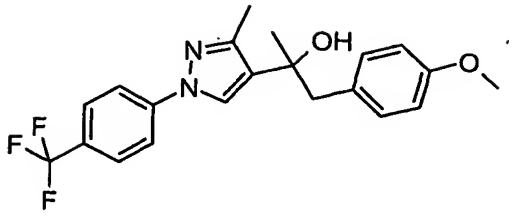
Example 150

2-Methyl-2-(4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-propionic acid



Step A

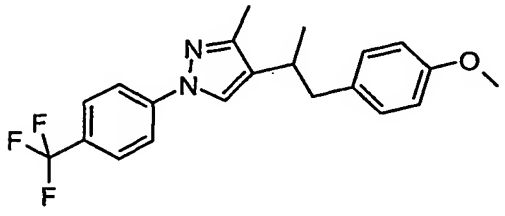
(R, S)-1-(4-Methoxy-phenyl)-2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-2-ol



To a solution of 1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (804 mg, 3mmol) in THF (20 mL) at -80 0C is added 4-methoxylbenzyl magnesium chloride (0.25 M in THF, 24 mL) and the mixture is stirred at ambient temperature overnight. It is quenched with 0.2 N HCl, extracted with EtOAc. The organic layer is concentrated to give the titled compound as an oil. This is used for the next reaction without further purification.
ESMS+: 391 (M+H)

Step B

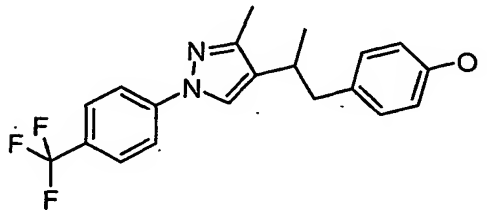
(R, S)-4-[2-(4-Methoxy-phenyl)-1-methyl-ethyl]-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole



To a solution of (R, S)-1-(4-methoxy-phenyl)-2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-2-ol (3 mmol) in dichloromethane (20 mL) at room temperature is added TFA (1.2 mL, 15 mmol) followed by Et3SiH (2.4 mL, 15 mmol). After 3 hours, it is quenched with saturated NaHCO3, extracted with dichloromethane. The organic layer is concentrated and purified by column chromatography (0-5% EtOAc in hexanes) to give a white solid. This is subjected to hydrogenation (5% Pd/C, 60 psi) in EtOH overnight. It is filtered and washed with EtOH. Combined filtrate is concentrated to give an oil: 760 mg (84%). This is used for the next reaction without further purification.

Step C

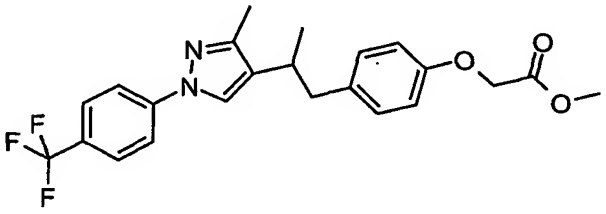
(R,S)-4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenol



(R, S)-4-[2-(4-Methoxy-phenyl)-1-methyl-ethyl]-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (760 mg, 2mmol) is treated with BBr3/CH2Cl2 (1M, 6 mL) from 0 0C to room temperature for 3 hours. It is quenched with MeOH and evaporated to dryness. The residue is purified by column chromatography (0-20% EtOAc in hexanes) to give the titled compound as a solid: 320 mg (44%)
ESMS-: 359 (M-1).

Step D

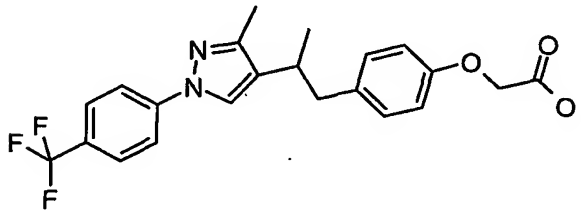
(R,S)-(4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-acetic acid methyl ester



A mixture of (R,S)-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenol (150 mg, 0.42 mmol), methyl bromoacetate (0.096 mL, 1 mmol) and potassium carbonate (172 mg, 1.26 mmol) in acetonitrile (7 mL) is stirred at reflux overnight. It is filtered and washed with EtOAc. The combined filtrate is concentrated and purified by column chromatography (0-20% EtOAc in hexanes) to give the titled compound: 135 mg (75%).
ESMS+: 433 (M+H).

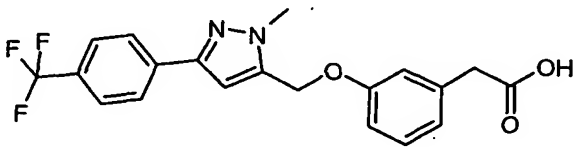
Step E

(R, S)-(4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-acetic acid



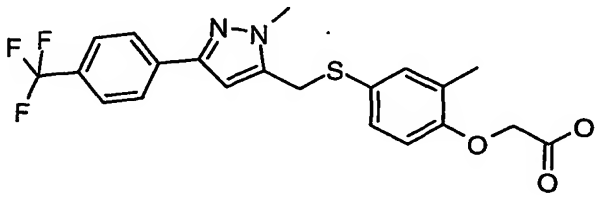
(R,S)-(4-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propyl}-phenoxy)-acetic acid methyl ester (135 mg, 0.3 mmol) is treated in a mixture of 2N LiOH/H2O and dioxane at 80 0C for 3 hours. Solvent is evaporated and the residue partitioned between EtOAc and 1N HCl. The organic layer is concentrated to give the titled compound as a solid: 126 mg (96%).
HRMS: Calcd. 419.1582, Found: 419.1594.

Example 151
{3-[2-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenyl}-acetic acid



HRMS: Calcd. 391.1270, found, 391.1253.

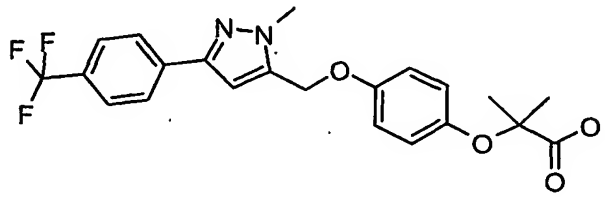
Example 152
{2-Methyl-4-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethylsulfanyl]-phenoxy}-acetic acid



HRMS: Calcd. 437.1147, found, 437.1144.

Example 153

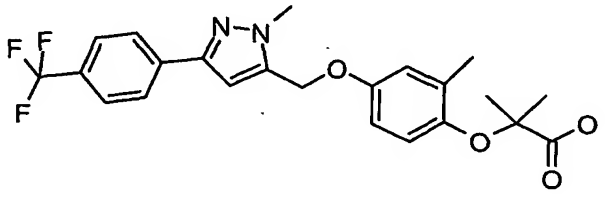
2-Methyl-2-{4-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenoxy}-propionic acid



HRMS: Calcd. 435.1532, found, 435.1527.

Example 154

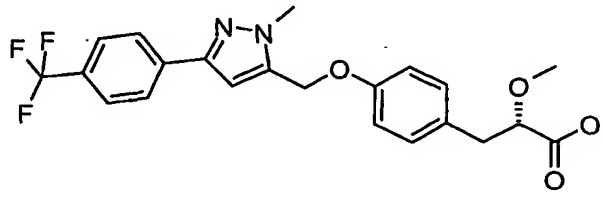
2-Methyl-2-{2-methyl-4-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenoxy}-propionic acid



HRMS: Calcd. 449.1688, found, 449.1690.

Example 155

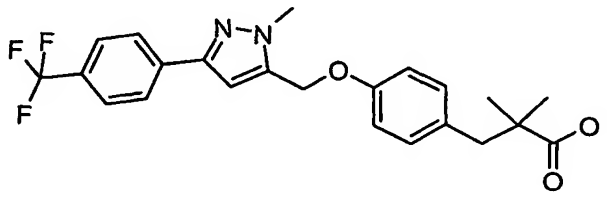
(S)-2-Methoxy-3-{4-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenyl}-propionic acid



HRMS: Calcd. 435.1532, found, 435.1544.

Example 156

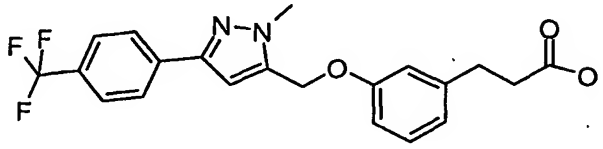
2,2-Dimethyl-3-{4-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenyl}-propionic acid



HRMS: Calcd. 447.1895, found, 447.1890.

Example 157

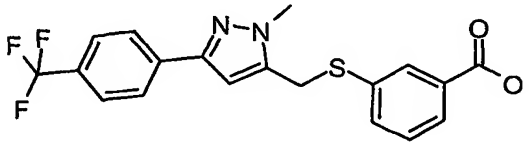
3-{3-[2-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethoxy]-phenyl}-propionic acid



HRMS: Calcd. 405.1426, found, 405.1413.

Example 158

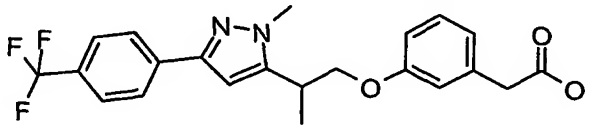
3-[2-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-ylmethylsulfanyl]-benzoic acid



HRMS: Calcd. 393.0884, found, 393.0875.

Example 159

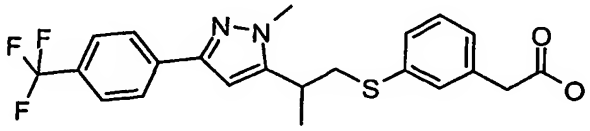
(R,S)-(3-{2-[2-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-propoxy}-phenyl)-acetic acid



HRMS: Calcd. 419.1582, found, 419.1583.

Example 160

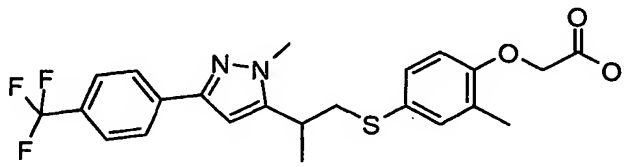
(R,S)-(3-{2-[2-Methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-propylsulfanyl}-phenyl)-acetic acid



HRMS: Calcd. 435.1354, found, 435.1351.

Example 161

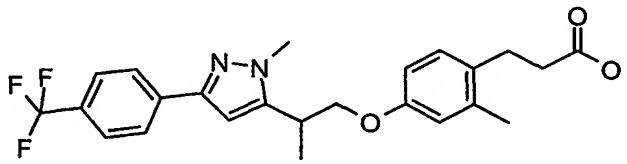
(R,S)-(2-Methyl-4-{2-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-propylsulfanyl}-phenoxy)-acetic acid



HRMS: Calcd. 465.1460, found, 465.1451.

Example 162

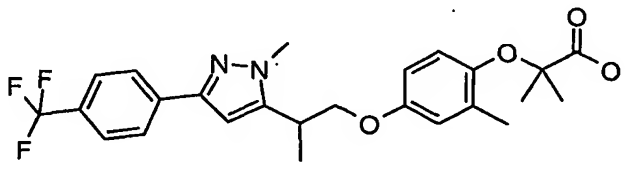
(R,S)-3-(2-Methyl-4-{2-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-propoxy}-phenyl)-propionic acid



HRMS: Calcd. 447.1895, found, 447.1873.

Example 163

(R,S)-2-Methyl-2-(2-methyl-4-{2-[2-methyl-5-(4-trifluoromethyl-phenyl)-2H-pyrazol-3-yl]-propoxy}-phenoxy)-propionic acid



HRMS: Calcd. 477.2001, found, 477.1989.

Biological Assays

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARα receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using SPA technology with PPAR receptors. Tritium-labeled PPARα agonists are used as radioligands for generating displacement curves and IC_{50} values with compounds of the invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs are constitutively expressed using plasmids containing the CMV promoter. For PPARα, interference by endogenous PPARγ in CV-1 cells is an issue. In order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPARα agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM).

These studies are carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"). These studies provide in vitro data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for

compounds of the invention are compared with corresponding data for marketed compounds that act on huPPARα.

The binding and cotransfection efficacy values for compounds of the invention which are especially useful for modulating a PPAR receptor, are ≤ 100 nM and ≥ 50%, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol Elevation in HuapoAI Transgenic Mice

Compounds of the present invention are studied for effects upon HDL and triglyceride levels in human apoAI mice. For each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME) are acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation, mice and chow are weighed and assigned to test groups (n = 5) with randomization by body weight. Mice are dosed daily by oral gavage for 8 days using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) is 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice are dosed daily between 6 and 8 a.m. with a dosing volume of 0.2ml. Prior to termination, animals and diets are weighed and body weight change and food consumption are calculated. Three hours after last dose, mice are euthanized with CO2 and blood is removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad are excised and weighed. Blood is permitted to clot and serum is separated from the blood by centrifugation.

Cholesterol and triglycerides are measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures are modified from published work (McGowan M. W. et al., Clin Chem 29:538-542,1983; Allain C. C. et al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and total cholesterol, respectively, commercial quality control plasma, and samples are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, added to a well containing 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature on a plate shaker and absorbance is read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples are applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol is monitored in the flow strem at 505 nm and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage

corresponding to change in cholesterol concentration is plotted vs time and the area under the curve corresponding to the elution of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) is calculated using Perkin Elmer Turbochrome software.

Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention is Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

The percent increase of HDLc serum levels in mice receiving a compound of the invention is compared to mice receiving vehicle to identify compounds of the invention that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30 mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

Evaluation of Glucose Levels in db/db Mice

The effects upon plasma glucose associated with administering various dose levels of different compounds of the present invention and the PPAR gamma agonist rosiglitazone (BRL49653) or the PPAR alpha agonist

fenofibrate, and the control, to male db/db mice, are studied.

Five week old male diabetic (db/db) mice [for example, C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates are housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample is discharged into a heparinized microtainer with gel separator and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose measured immediately. Remaining plasma is frozen until the completion of the experiment, when glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After the 24-hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes,

chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

Glucose is measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures are modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified in our laboratory for use in a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances are compared to a standard curve (100-800 for glucose). Values for the quality control sample are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment

are assayed at the same time to minimize inter-assay variability.

Evaluation of the Effects of Compounds of the Present Invention upon A^y Mice Body Weight, Fat Mass, Glucose and Insulin Levels

Female A^y Mice

Female A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty weeks of age the mice are randomly assigned to vehicle control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights are measured daily throughout the study. On day 14 mice are maintained in individual metabolic chambers for indirect calorimetry assessment of energy expenditure and fuel utilization. On day 18 mice are again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass are evaluated and suggest which compounds of this invention can be especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealing a significant reduction in respiratory quotient (RQ) in treated animals during the dark cycle [0.864 ± 0.013 (Control) vs. 0.803 ± 0.007 (Treated); $p < 0.001$] is indicative of an increased utilization of fat during the

animals' active (dark) cycle and can be used to selected especially desired compounds of this invention. Additionally, treated animals displaying significantly higher rates of energy expenditure than control animals suggest such compounds of this invention can be especially desired.

Male KK/A^y Mice

Male KK/A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the mice are randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days. Plasma glucose, triglyceride, and insulin levels are assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to identify compounds of this invention which may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g are placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Under these conditions, hamsters become hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow have a total plasma

cholesterol level between 100-150 mg/dl.) Hamsters with high plasma cholesterol (180 mg/dl and above) are randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

A Compound of this invention is dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by garvage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) is given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control is vehicle alone. Dosing is performed daily in the early morning for 14 days.

Quantification of Plasma Lipids :

On the last day of the test, hamsters are bled (400 ul) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples are collected into heparinized microfuge tubes chilled in ice bath. Plasma samples are separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides are determined by means of enzymatic assays carried out automatically in the Monarch equipment (Instrumentation Laboratory) following the manufacturer's precedure. Plasma lipoproteins (VLDL, LDL and HDL) are resolved by injecting 25 ul of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids are accomplished by postcolumn incubation of the effluent with a Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed is

proportional to the cholesterol concentration and is measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group. Especially desired compounds are markedly more potent than fenofibrate in LDL-lowering efficacy. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention is also studied. The data for reduction in total cholesterol and triglyceride levels after treatment with a compound of this invention for 14 days is compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

Method to Elucidate the Fibrinogen-Lowering Effect of PPAR Modulators

Zucker Fatty Rat Model:

The life phase of the study on fibrinogen-lowering effect of compounds of this invention is part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14^{th}) day of the treatment period, with the animals placed under surgical anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that is stored at -70 °C prior to fibrinogen assay.

Quantification of Rat Plasma Fibrinogen:

Rat plasma fibrinogen levels are quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In essence, 100 ul of plasma is sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard concentration) is then added. The instrument monitors the clotting time, a function of fibrinogen concentration quantified with reference to standard samples. Compounds that lower fibrinogen level greater than vehicle can be especially desired.

Cholesterol and triglyceride lowering effects of compounds of this invention are also studied in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat[1] or ZDF Rat[2] Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and weight are acclimated for 1 week prior to treatment. Rats are on normal chow and water is provided ad libitum throughout the course of the experiment.

Compounds of this invention are dissolved in an aqueous vehicle such that each rat received once a day approximately 1 ml of the solution by garvage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist given at doses of 300 mg/kg, as well as the vehicle are controls. Dosing is performed daily in the early morning

for 14 days. Over the course of the experiment, body weight and food consumption are monitored.

Using this assay, compounds of this invention are identified to determine which can be associated with a significant weight reduction.

Method to elucidate the activation of the PPAR delta receptor *in vivo*

This method is particularly useful for measuring the in vivo PPARdelta receptor activation of compounds of this invention that are determined to possess significant in vitro activity for that receptor isoform over the PPAR gamma isoform.

Male PPARa null mice (129s4 SvJae-PPARa<tm1Gonz> mice; Jackson Laboratories) of 8-9 weeks of age are maintained on Purina 5001 chow with water ad libitum for at least one week prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Using the GroupOptimizeV211.xls program, mice are randomized into treatment groups of five animals each based on their body weight.

Compounds of this invention are suspended in an aqueous vehicle of 1% (w/v) carboxymethylcellulose and 0.25% Tween 80 such that each mouse receives once a day approx. 0.2 ml of the solution by gavage at doses ranging from 0.2 to 20 mg/kg body weight. A control group of mice is included in each experiment whereby they are dosed in parallel with vehicle alone. Dosing is performed daily in the early morning for 7 days.

On the last day of dosing, mice are euthanized by CO2 asphyxiation 3 hours after the final dose. Blood samples are collected by heart draw into EDTA-containing microfuge tubes and chilled on ice. Liver samples are collected by necropsy and are flash-frozen in liquid nitrogen and stored

at -80 degrees Celsius. For RNA isolation from liver, five to ten mg of frozen liver is placed in 700 µl of 1x Nucleic Acid Lysis Solution (Applied Biosystems Inc., Foster City, CA) and homogenized using a hand-held tissue macerator (Biospec Products Inc., Bartlesville, OK). The homogenate is filtered through an ABI Tissue pre-filter (Applied Biosystems Inc., Foster City, CA) and collected in a deep well plate on an ABI 6100 Nucleic Acid prep station (Applied Biosystems Inc., Foster City, CA). The filtered homogenate is then loaded onto an RNA isolation plate and the RNA -- Tissue-Filter-DNA method is run on the ABI 6100. The isolated RNA is eluted in 150 µl of RNase free water. For quality assessment, 9 µl of the isolated RNA solution is loaded onto a 1% TBE agarose gel, and the RNA is visualized by ethidium bromide fluorescence.

Complementary DNA (cDNA) is synthesized using the ABI High Capacity Archive Kit (Applied Biosystems Inc., Foster City, CA). Briefly, a 2x reverse transcriptase Master Mix is prepared according to the manufacturer's protocol for the appropriate number of samples (RT Buffer, dNTP, Random Primers, MultiScribe RT (50U/µl), RNase free water). For each reaction, 50 µl of 2x RT Master Mix is added to 50 µl of isolated RNA in a PCR tube that is incubated in a thermocycler (25°C for 10 minutes followed by 37°C for 2 hours). The resultant cDNA preparation is diluted 1:100 in dH2O for analysis by real-time PCR. Also, a standard curve of cDNA is diluted 1:20, 1:100, 1:400, 1:2000, 1:10,000 for use in final quantitation.

A real-time PCR Master Mix for mouse Cyp4A1 gene expression is mixed to contain:

- 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)

- 6 micromolar final concentration Forward primer; Qiagen/Operon Technologies, Alameda, CA)
- 6 micromolar final concentration Reverse primer (Qiagen/Operon Technologies, Alameda, CA)
- 0.15 micromolar final concentration Probe (5' 6-FAM and 3' Tamra-Q; Qiagen/Operon Technologies, Alameda, CA)
- RNase free water to 10 microliters

A real-time PCR Master Mix for the 18S ribosomal RNA control gene expression is mixed to contain

- 1X Taqman Universal PCR Master Mix (Applied Biosystems Inc., Foster City, CA)
- 0.34 micromolar Probe/Primer TaqMan® Ribosomal RNA Control Reagents #4308329 Applied Biosystems Inc., Foster City, CA)
- RNase free water to 10 microliters

For the real-time PCR analysis, 6 ul of the respective Master Mix solution (either Cyp4A1 or 18S) and 4 ul either of diluted cDNA or of Standard Curve samples is added to individual wells of a 384-well plate (n = 2 for Standards; n = 4 for unknowns). Reactions are performed using the ABI 7900 HT standard universal RT-PCR cycling protocol. Data are analyzed using SDS 2.1 (Applied Biosystems Inc., Foster City, CA). Average quantity and standard deviation are calculated automatically for each individual sample, according to the standard curve values. Using Microsoft

Excel 2000, mean values for each group of five individual mice is calculated. The mean value of each compound-treated group is divided by the mean value of the vehicle-treated group. The fold induction over the vehicle group is determined by assigning the vehicle group to the value of 1.0, and the fold change of the mean value for each group is expressed as fold-induction versus vehicle (1.0). Data are plotted using Jandel SigmaPlot 8.0.

Monkey studies

Efficacy Studies

Compounds of the invention may be examined in a dyslipidemic rhesus monkey model. After an oral dose-escalation study for 28 days in obese, non-diabetic rhesus monkeys a determination of HDL-c elevation is made with each dose and compared with pretreatment levels. LDL cholesterol is also determined with each dose. C-reactive protein levels are measured and compared to pretreatment levels.

Compound of Formula 1 may be shown to elevate plasma HDL-cholesterol levels in an African Green Monkey model in a manner similar to that described above in rhesus monkeys.

Two groups of monkeys are placed in a dose-escalating study that consists of one week of baseline measurements, 9 weeks of treatments (vehicle, Compound of Formula I), and four weeks of washout. During baseline, monkeys in all three groups are administered vehicle once daily for seven days. Test compound of Formula I, is administered in vehicle once daily for three weeks, then at a greater concentration

(double the dose may be desired) once daily for three weeks, and then a still greater concentration (double the most recent dose may be desired) once daily for three weeks. At the completion of treatment, monkeys in both groups are administered vehicle once daily and monitored for an additional six weeks.

Animals are fasted overnight and then sedated for body weight measurements and blood collection at weeks 1 (vehicle), 2, 3, 4, 6, 7, 9, 10, 12, and 14 of the study.

Parameters to measured, for example:
Body weight
Total plasma cholesterol
HDL
LDL
Triglycerides
Insulin
Glucose
PK parameters at week 4, 7, and 10 (plasma drug concentration at last week of each dose)
ApoAI
ApoAII
ApoB
ApoCIII
Liver enzymes (SGPT, SGOT, □GT)
Complete blood count

Additionally, other measures may be made, as appropriate, and consistent with the stated study design.

EQUIVALENTS:

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.